

**CORRELATION OF SONOGRAPHIC FINDINGS
WITH TECHNETIUM PERTECHNETATE UPTAKE
OF THYROID GLAND IN PRIMARY
HYPERTHYROID PATIENT**

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**DISSERTATION SUBMITTED IN PARTIAL
FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF MEDICINE (RADIOLOGY)**



**UNIVERSITI SAINS MALAYSIA
2022**

ACKNOWLEDGEMENT

First and foremost, I would like to express my gratitude to Almighty Allah SWT. The completion of this thesis would not have been possible without His blessings and grace. The completion of this thesis would also not have been possible without the participation, cooperation, and assistance of so many people whose names may not all be enumerated.

Their contribution is sincerely appreciated and gratefully acknowledged. However, I would like to express my deepest and utmost appreciation, particularly to the following:

1. Dr Ahmad Hadif Zaidin Samsudin, my supervisor, provided continuous assistance and guidance in completing this thesis. Dr Norazlina Mat Nawati (my co-supervisor) always supported and guided me in completing the thesis.
2. Prof Madya. Dr. Mohd Shafie Abdullah, Prof Madya. Dr. Mohd Ezane Aziz, Prof Madya. Dr Juhara Haron, Dr Khairil Amir Sayuti, Dr Chandran a/l Nadarajan, Dr Wan Aireene Wan Ahmed, Dr Nur Asma Sapiai, Dr Nasibah Mohamad, and to all of whom directly or indirectly contributed their ideas, comments, and support in the completion of this study.
3. En Mohamad Yusri bin Udin, colleagues and staff at the Department of Nuclear Medicine, Radiotherapy and Oncology, Hospital USM.
4. My beloved parents, husband, and children.

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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

PSV	Peak systolic velocity
TcTU	Technetium Pertechnetate thyroid uptake
TRH	Thyrotropin-releasing hormone
TSH	Tyrosine stimulating hormone
RAI	Radioactive iodine
T4	Thyroxine
T3	Triiodothyronine
RAIU	Radioactive iodine uptake index
USM	Universiti Sains Malaysia
USG	Ultrasound
TV-USG	Total volume ultrasound
TV-Tc	Total volume technetium study

ABSTRAK

Pendahuluan: Radioaktif Iodin (RAI) telah digunakan sejak tahun 1941. Walaupun ianya telah lama wujud dan menjadi kaedah penting dalam merawat hipertiroidisme, masih ada perdebatan mengenai kaedah pemberian dos nya. Penyerapan technetium pertechnetate oleh kelenjar tiroid telah digunakan secara meluas sebagai siasatan awal sebelum memutuskan dos sebenar terapi radioiodine. Selain menyebabkan radiasi tambahan kepada pesakit, kajian penyerapan tiroid technetium pertechnetate juga menyebabkan kos tambahan kepada pesakit. Ultrabunyi telah menjadi salah satu modaliti penting dalam menilai kelenjar tiroid. Ia adalah kos efektif, tidak menghasilkan radiasi pengionan dan boleh menentukan status morfologi dan vaskularity kelenjar tiroid. Kajian ini bertujuan untuk menentukan korelasi kajian ultrabunyi (USG) kelenjar tiroid dengan nilai penyerapan technetium pertechnetate tiroid (TcTU).

Kaedah: Satu kajian keratan lintang telah dijalankan di Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan. Seramai 17 pesakit yang menjalani imbasan TcTU untuk rawatan RAI yang memenuhi kriteria kemasukan dan pengecualian telah dimasukkan ke dalam kajian. Semua pesakit tertakluk kepada ultrabunyi sebelum imbasan TcTU. Data demografi subjek dikumpulkan dan dianalisis menggunakan analisis deskriptif dan dibentangkan sebagai kekerapan dan peratusan. Semasa USG, parameter isipadu tiroid (TV-USG) dan halaju systolic puncak arteri tiroid (PSV) telah direkodkan, dan data dibentangkan sebagai sisihan min dan piawai. Semasa imbasan TcTU, parameter untuk isipadu tiroid (TV-Tc) dan pengambilan peratusan TcTU telah direkodkan, dan data dibentangkan sebagai sisihan min dan piawai. Korelasi Spearman digunakan untuk mengaitkan penemuan USG dan TcTU kerana data taburan tidak normal.

Keputusan: Min umur subjek adalah 41.29 (14.01), dengan majoriti subjek adalah wanita (n: 12, 70.6%). Jumlah purata min isipadu tiroid TV-USG adalah 34.63 (22.10) ml, dan TV-Tc adalah 43.41 (24.02) ml. PSV kelenjar tiroid adalah 41.64 (12.81) cm/s, dan peratusan penyerapan TcTU adalah 15.58 (12.65) %. Terdapat korelasi positif yang kuat antara TV-USG dan TV-Tc dan korelasi positif sederhana antara PSV dan peratusan penyerapan TcTU ($p < 0.05$).

Kesimpulan: Kajian kami menunjukkan korelasi positif yang sangat signifikan antara isipadu kelenjar tiroid dan korelasi positif sederhana antara penemuan PSV ultrabunyi kelenjar tiroid dan kajian peratusan penyerapan technetium. Oleh itu, ultrabunyi boleh memainkan peranan dalam meramalkan dos dan hasil rawatan RAI.

Kata kunci: Hipertiroid, Technetium pertechnetate, Kadar penyerapan Technetium, Puncak halaju sistolik

ABSTRACT

Introduction: Radioactive iodine (RAI) has been used since 1941. Despite its long existence and has become a mainstay in treating hyperthyroidism, there's still debate regarding its dosing method. Technetium pertechnetate thyroid uptake study had been widely used as a preliminary investigation before deciding the actual dose of radioiodine therapy. Besides causing extra radiation to the patient, the technetium pertechnetate thyroid uptake study also caused an additional cost to the patient. Ultrasound has been one of the essential modalities in assessing the thyroid gland. It is a cost-effective, non-radiation study and can determine both the morphological and vascularity status of the thyroid gland. This study aims to determine the correlation of thyroid gland sonographic study (USG) with the value of technetium pertechnetate thyroid scan (TcTU).

Methods: A prospective cross-sectional study was conducted in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan. A total of 17 patients who underwent their TcTU scan for RAI treatment that fulfilled the inclusion and exclusion criteria were included in the study. All patients were subjected to ultrasound prior to the TcTU scan. The subjects' demographic data were collected and analysed using descriptive analysis and were presented as frequency and percentage. During USG, the thyroid volume (TV-USG) parameter and superior thyroid artery peak systolic velocity (PSV) was recorded, and data were presented as mean and standard deviation. During the TcTU scan, the parameter for TcTU volume (TV-Tc) and TcTU percentage uptakes were recorded, and data were presented as mean and standard deviation. Spearman correlation was used to correlate USG and TcTU findings as the data are not normally distributed.

Results: Subjects' mean age was 41.29 (14.01), with most of the subjects being female (n:12, 70.6%). The mean volume of TV-USG was 34.63 (22.10) ml, and TV-Tc was 43.41 (4.02) ml. The PSV of the thyroid gland was 41.64 (12.81) cm/s, and the percentage of TcTU uptake was 15.58 (12.65) %. There is a strong positive correlation between TV-USG and TV-Tc and a moderate positive correlation between PSV and percentage TcTU uptake ($p < 0.05$).

Conclusion: Our study showed a significant positive correlation of volume measurement and a moderate correlation between peak systolic velocity and percentage thyroid uptake between the sonographic findings and the TcTU study. Thus, an ultrasound may play a role in predicting the possible dosage and outcome of the RAI treatment.

Keywords: Hyperthyroidism, technetium pertechnetate, Technetium uptake study, Peak systolic velocity.

CHAPTER 1: BACKGROUND

1.1 Introduction

Hyperthyroidism is a common endocrine disorder. Based on the prevalence of thyroid disorders and thyroid autoantibodies in the coastal communities of Malaysia, the prevalence of overt hyperthyroid is 3.4 per 1000 population, which is predominantly women (Shahar *et al.*, 2015). An increase in thyroid hormone will cause an increase in systemic metabolism, thus leading to an increase in cardiac contractility and heart rate. Persistent hypercontractility and tachycardia lead to cardiomyopathy and cardiac hypertrophy, contributing to morbidity.

Currently, there are three approaches used to treat the disease namely, pharmacological treatment with antithyroid drugs, radioactive iodine therapy (RAI), and surgical removal of the thyroid gland; the latter two treatments are considered the definitive treatment. The treatment aims to achieve euthyroid or hypothyroid status with no relapses. There is no long-term difference in the quality of life amongst patients who received these treatments (Zainudin *et al.*, 2012). The treatment should be decided individually and patient preference.

RAI therapy has been a well-established treatment for benign and malignant thyroid disorders. However, the major drawback of RAI is that it can exaggerate the transient hyperthyroid symptoms and worsen thyroid ophthalmopathy. It is contraindicated in severe thyrotoxicosis patients, pregnancy, and breastfeeding women. Iodine therapy aims to deliver the maximum radiation absorbed dose to achieve adequate ablation and destruction of thyroid cells. The loss of functional thyroid tissue will lead to hypothyroidism in most patients. Thyroid function usually normalised within 3-12 months after RAI therapy while thyroid gland size within 1-year post-treatment (Kahaly *et al.*, 2018).

There are two methods for delivering RAI therapy dose: empirical fixed dose regime, 370-550 MBq (10-15 mCi), or corrected dosage based on thyroid gland size and activity. Recent literature supports that corrected dose is better compared to empirical fixed dose and the European Association of Nuclear Medicine also recommends the usage of it (Kahaly *et al.*, 2018). Radioactive iodine uptake index (RAUI) study had been the gold standard in evaluating thyroid gland activity. However, the RAUI result can be influenced by an iodine-containing diet and medication as well as its duration of measurement that can up to 24 hours can be irksome and time-consuming; both to patient and managing team. Some literatures suggest that technetium pertechnetate has offered greater convenience to patient and better outcomes. There is also no meticulous preparation for the patient, and image acquisition can be made after 20 minutes post-injection of technetium. However, the technetium study poses extra-radiation and extra cost to patients.

Preferably, all patients subjected to radioactive iodine therapy should do the thyroid uptake scan for dose calculation to ensure each patient receives the appropriate dosage for adequate ablation. However, due to its limited availability, time-consuming, costly, and added to extra radiation dose, the thyroid uptake study is commonly replaced with empirical fixed dose instead.

Another tool that is sensitive in assessing the thyroid gland is ultrasound. It is easily accessible and non-ionising radiation study. It can determine both the morphological and vascularity status of the thyroid gland. In hyperthyroid patients, the hemodynamic changes are observed due to excess in thyroid hormone production. High intraparenchymal peak systolic velocity value indicates hyperthyroidism since it reflects a sustained stimulation on a thyroid gland capable of producing and secreting excess thyroid hormone (Bogazzi *et al.*, 1999).

This study aims to determine any correlation of thyroid gland sonographic study with technetium pertechnetate thyroid scan value. We aim to determine whether there is any role of ultrasound study before RAI therapy replacing the technetium study.

1.2 Objective

1.2.1 General Objective

To study the sonographic findings and the technetium pertechnetate uptake of the thyroid gland in the primary hyperthyroid patient.

1.2.2 Specific Objective

1. To determine the mean sonographic thyroid volume and peak systolic velocity of superior thyroid artery in the hyperthyroid patient using ultrasound.
2. To determine the mean thyroid volume and percentage of uptake value using technetium pertechnetate scan.
3. To determine the correlation between mean sonographic thyroid volume with technetium pertechnetate thyroid volume.
4. To determine the correlation between the peak systolic velocity superior thyroid artery with the thyroid percentage of uptake in the technetium pertechnetate scan.

1.3 Hypothesis

The expected measurement of peak systolic velocity superior thyroid artery and the anticipated measurement of technetium pertechnetate in a hyperthyroid patient is high. There is a significant correlation between the peak systolic velocity of the superior thyroid artery and Technetium Pertechnetate thyroid uptake (TcTU) percentage.

1.4 Research question

- 1 What is the expected finding of peak systolic velocity superior thyroid artery in a hyperthyroid patient?
- 2 What is the expected measurement of technetium pertechnetate uptake in a hyperthyroid patient?
- 3 What is the correlation between peak systolic velocity of superior thyroid artery and Technetium Pertechnetate thyroid uptake study?

CHAPTER 2: LITERATURE REVIEW

2.1 Overview of the Thyroid gland

The thyroid gland is a butterfly-shaped organ found in the anterior part of the neck region. A highly vascularized organ receives blood supply from bilateral superior and inferior thyroid arteries. The superior thyroid artery is a branch of the external carotid artery which descend towards the thyroid gland and supply the superior and anterior portion of the thyroid gland. The inferior thyroid artery originates from the thyrocervical trunk, branches from the subclavian artery. It ascends superomedially and supplies the posteroinferior part of the thyroid gland. The gland contains follicular cells that release thyroid hormone (T3/T4) in response to complex hypothalamus-pituitary-thyroid axis feedback. The thyroid hormone production starts with thyrotropin-releasing hormone (TRH) from the hypothalamus, stimulating the anterior pituitary to release tyrosine stimulating hormone (TSH). The binding of TSH to its receptors in thyroid follicle cells will release the thyroid hormones, thyroxine (T4) primarily, and a small amount of triiodothyronine (T3). Sequentially, the elevation of these hormones will send negative feedback to the hypothalamus to stop the TRH stimulation to the pituitary gland, thus halting the production of TSH.

Synthesis of thyroid hormone requires dietary iodine. Active transport of iodide ions into the cells by iodide transporter then undergoes oxidation that results in iodine. Later, iodine will link to the tyrosine amino acids in thyroglobulin via peroxidase enzyme through organification. This produces two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodine. These intermediaries are coupled via covalent bonds that result in the compound of T3 or T4, thyroid hormone, with three or four iodine compounds. These are stored in the thyroid follicular lumen. Thyroid hormone controls the rate of cell metabolism and activity. Any disruption in thyroid hormone

production will affect the balance of cells metabolism, and activity thus will lead to systemic symptoms.

2.2 Hyperthyroidism, diagnosis, and treatment

Hyperthyroidism is a clinical condition due to inappropriate high synthesis and secretion of thyroid hormone. It is a clinical syndrome characterised by a hypermetabolic state caused by increased free serum T4 and occasionally free T3. It can be divided into primary hyperthyroidism and secondary hyperthyroidism. Primary hyperthyroidism is caused by thyroid gland malfunctionings such as hyperplasia and overstimulation of thyroid epithelium or acute destruction of thyroid follicles that causes overproduction of thyroid hormone. Meanwhile, secondary hyperthyroidism is caused by external factors that cause thyroid gland dysfunction, such as pituitary adenoma or Struma ovary tumour.

Hyperthyroidism is diagnosed based on various clinical symptoms, namely unexplained weight loss with increased appetite, goitre, palpitation, sweating, heat intolerance, nervousness, changes in bowel movement, or thin and dry hair. The patient may also present with heart failure symptoms, atrial fibrillation, or periodic hypokalaemic paralysis. To confirm the diagnosis, a blood investigation measuring free T4, T3, and TSH levels should be taken.

In Malaysia, hyperthyroidism is one of the commonest endocrine disorders. Based on the prevalence of thyroid disorders and thyroid autoantibodies in the coastal communities of Malaysia, the prevalence for overt hyperthyroid is 3.4 per 1000 population, which predominantly women (Shahar *et al.*, 2015). Long-standing untreated or partially treated hyperthyroidism will cause weight loss, osteoporosis, muscle weakness, neuropsychiatric symptoms, and hemodynamic changes, including increased heart rate and cardiac contractility, atrial fibrillation, and embolic events (Bogazzi *et al.*, 1999; Silberstein *et al.*, 2012; Ross *et al.*, 2016). An ideal treatment for hyperthyroid is

the one that should restore the normal thyroid hormone level and prevent relapse or hypothyroidism development post-treatment. However, there is no such treatment available at this moment. Currently, three primary treatment options for hyperthyroidism are anti-thyroid drugs, radioactive iodine therapy, and surgery. In Malaysia, the anti-thyroid drug is used as a primary treatment for hyperthyroid patients, especially in the elderly, those with high surgical risk or those unable to follow radiation safety regulations, and patients with moderate to severe grave's disease (Zainudin *et al.*, 2012). The anti-thyroid drug should be tapered off after being maintained for 12-18 months of treatment. The remission rate of over 50% is seen especially in a female with mild disease, small goitre, and low thyrotropin receptor antibody (Zainudin *et al.*, 2012). A common side effect of the anti-thyroid drug includes rash, urticaria, and arthralgia. An anti-thyroid drug's rare but dangerous side effect would be agranulocytosis, which occurs in 0.1-1.0% (Kahaly *et al.*, 2018). Surgical removal of the thyroid gland is indicated in failed medical therapy, goitres with pressure effects, suspected malignancy, and severe ophthalmopathy. The complications of thyroidectomy include the risk of recurrent laryngeal nerve palsy and the risk of postoperative hypoparathyroidism (Kahaly *et al.*, 2018), which occur in at least 1-2% of patients (Hegedüs, 2009).

Radioactive iodine therapy has been used since 1941. Iodine – 131 (I^{131}) is a beta emitter radionuclide. It is considered effective, safe, and relatively inexpensive (Hegedüs, 2009). The principle of radioiodine therapy is based on physiological uptake and metabolism of iodine in the thyroid gland, whereby I^{131} will be taken up by iodine transporter into the thyroid gland. Consequently, the beta-particle release by I^{131} will destroy the follicular cells (Zaid Zaniel, Manap and Hamzah, 2016). A common indication for radioiodine therapy in benign thyroid disorder such as graves' disease, toxic

multinodular goitre or toxic adenoma who are failed medical treatment, thyroid cardiomyopathy, and those who developed hypokalaemic periodic paralysis.

The outcome of the radioiodine treatment strongly depends on the size of the thyroid, the radioiodine uptake, degree of thyrotoxicosis on treatment, and activity of radioiodine administered (Burch and Cooper, 2015). As I^{131} acts slowly, a second dose should not be given before six months (Burch and Cooper, 2015). Despite its long existence and has become a mainstay in treating hyperthyroidism, there's still debate regarding its dosing method. A high dose of I^{131} will cause rapid destruction of the thyroid gland, leading to increased incidence of hypothyroidism, and require the patient to depend on lifelong hormonal therapy. Meanwhile, a low dose of I^{131} will delay achieving hypothyroidism and prolong the effect of thyroid hormone and a higher recurrence rate of failed treatment (De Rooij *et al.*, 2009). Several techniques are used to deliver an adequate radiation dose to the thyroid gland; these include dose calculation based on thyroid volume and thyroid iodine uptake and empirical fixed-dose approach (Mumtaz *et al.*, 2009). However, recent meta-analysis supports that the calculated dose had a better outcome than the empirical fixed-dose (Yeong Fong, Lutfi Shuaib and Hamzah, 2018). The European Association of Nuclear Medicine (EANM) guideline also recommended that individually calculated dose in patients aged <45 years of age, especially children (Stokkel *et al.*, 2010). The calculated dose of radioiodine therapy in Malaysia showed an 82.1% cure rate at six months post-treatment (Yeong Fong, Lutfi Shuaib and Hamzah, 2018).

The calculated dose aims to give the optimal dose of Iodine-131 that cause the patient to be euthyroid or avoid repeat treatment (Mumtaz *et al.*, 2009). In Hospital USM, the radioiodine therapy dose administered to the patient is calculated using the modified Marinelli's formula:

$$A \text{ (MBq)} = \frac{25 \times m(g) \times D \text{ (G)}}{[17.72 \times \ln (\text{TcTU percentage uptake}) + 30.4] \times 5.5}$$

m: mass of thyroid gland calculated

D: absorbed dose of technetium pertechnetate

2.3 Radioactive iodine uptake index and technetium pertechnetate uptake study

Radioactive iodine uptake index (RAUI) assay had been the gold standard in evaluating the activity of the thyroid gland. Through this study, nuclear medicine physicians can obtain information regarding the thyroid iodine uptake function and the size of the thyroid gland. It is done before the treatment of radioiodine therapy for dose calculation of radioactive iodine treatment. It can also differentiate causes of thyrotoxicosis either due to hyperactive production or destruction of the thyroid gland. It requires meticulous patient preparation as an iodine-containing diet will influence it. This study assesses the thyroid uptake at 24-hour intervals using a gamma counter or probe. It releases beta radiation and high gamma energy (364keV) (Szumowski *et al.*, 2016). This can be tiresome and time-consuming. Thus, some centres use Technetium Pertechnetate thyroid uptake (TcTU) as an alternative.

Technetium pertechnetate has a similar molecular weight to iodine; it can mimic the compound of iodine and transport it to thyroid tissue. It is not organified; thus, it is not retained in the thyroid gland. Therefore, the acquisition time is much faster than the RAUI assay study. Image acquisition can be made after 20 minutes post-injection using single-photon-emission computed tomography (SPECT) and does not require special patient preparation (Silberstein *et al.*, 2012). It is a pure gamma emitter with lower energy than iodine (140 keV) (Szumowski *et al.*, 2016). The effective dose of technetium pertechnetate is about 0.13 mSv, which is much lower compared to Iodine-131, which is about 6.6mSv. More radiation dose will be added in the technetium uptake study as we

will proceed with low dose computed tomography (CT) for 3-D valuation for volume calculation which contributes 1.5 to 2 mSv additional dose.

In Hospital USM, due to limited equipment and software to validate the iodine uptake, the technetium pertechnetate uptake study is used as a preliminary scan before deciding the actual dose of radioiodine therapy. The normal value for the RAUI study is 10% to 30%, and TcTU is 0.3% to 4.5%. Higher RAUI and TcTU uptake was observed in a hyperthyroid patient caused by overstimulation of thyroid hormone by follicle cells. Low or near zero uptakes in hyperthyroid patients are caused by acute destruction of thyroid follicles (Silberstein *et al.*, 2012).

2.4 Sonographic findings in hyperthyroidism

Ultrasound has been one of the essential modalities in assessing the thyroid gland. It can identify the presence of focal or diffused disease. The assessment can be done qualitative or quantitative. The normal thyroid gland has homogenous echogenicity due to high acoustic impedance between thyroid cells and thyroid colloid, easily discernible from adjacent muscular structures. The thyroid gland will appear heterogeneous hypoechoic in hyperthyroid patients due to hypervascularity and hypercellularity (dos Santos *et al.*, 2014).

Ultrasound is usually done to look for the morphology of the thyroid gland, and it is helpful in differentiated causes of thyrotoxicosis. A recent study by Zhao et al. (2012) and Hiraiwa et al. (2013) suggest that we can differentiate the cause of thyrotoxicosis by using colour doppler sonography findings.

In this study, we will be focusing on hyperthyroid caused by hyperplasia and overstimulation of thyroid epithelium or follicles. The initiating factors that trigger this condition are unknown. However, biological and environmental factors are the triggering factor that activates the inflammatory cascade, causing abnormal TSH receptor stimulator

and altering thyroid epithelial cells' behaviour (Smith and Hegedüs, 2016). This will cause hypertrophy and hyperplasia of thyroid epithelial cells and change the normal thyroid gland morphology, vascularity, and physiology.

Bogazzi et al. (1999) suggest that TSH can cause thyroidal angiogenesis, which is caused by amplified expression of growth factor of vasculotropins and tyrosine kinase receptors in turn act on endothelial cells. Bogazzi et al. (1999) also found a high peak systolic value in hyperthyroidism, suggestive of sustained stimulation on the thyroid gland. An increase in intrathyroidal vascularity is observed in those with stimulation of the thyroid gland and not due to destructive causes. Vita et al. (2019) found that thyroid vascularity corresponds to thyroid volume.

As mentioned earlier, an increase in vascularity was observed in hyperthyroidism caused by stimulation of the thyroid gland. Colour doppler assessment will show an increase in vascularity seen in the hyperthyroid patient. Apart from direct visualisation of increase in vascularity, spectral analysis of peak systolic velocity (PSV) of either superior thyroid artery or inferior thyroid artery can be done. According to dos Santos et al. (2014), there is no significant difference between superior and inferior thyroid arteries and both sides measurements. Thus, in our study, we will be measuring PSV of the superior thyroid artery in this study as its location is more superficial, easily identified as the first branch from the external carotid artery and rarely had variation in comparison with the inferior thyroid artery (Zhao *et al.*, 2012).

Few studies had used colour doppler flow of the thyroid gland as a tool in differentiating causes of thyrotoxicosis (Silberstein *et al.*, 2012; Zhao *et al.*, 2012). Hyperthyroidism caused by stimulation of the thyroid gland showed association with an increase in intrathyroidal vascularity as in Graves' disease or toxic adenoma. This condition is not seen to be present in thyrotoxicosis caused by exogenous ingestion and

destruction of the thyroid gland, such as thyroiditis or amiodarone induce thyrotoxicosis (Bogazzi *et al.*, 1999). The Society of Nuclear Medicine and Molecular Imaging guideline recommended that ultrasound doppler flow study can be used to distinguish causes of hyperthyroid, especially in those contraindicated for radioiodine or technetium study.

Joish *et al.* (2018) stated that the normal mean PSV of superior thyroid artery for euthyroid adults is 16.94 ± 5.3 cm/s with no significant difference between gender. Macedo *et al.* (2007), study shows a mean PSV of 25.84 cm/s in euthyroid adults. Most of the authors took the value of more than 50 cm/s as the ideal cut-off value for the hyperthyroid patient (Zhao *et al.*, 2012; dos Santos *et al.*, 2014).

2.5 Peak systolic velocity

Peak systolic velocity is a non-invasive quantitative measurement of arterial blood flow velocity, widely used as a predictive factor of various diseases. Peak systolic velocity is influenced mainly by the resistance of the distal arterial bed and compliance of the vessels (Halpren, Merton and Forsberg, 1998).

As discussed earlier, in hyperthyroid disease, caused by hyperplasia or overstimulation of the thyroid gland, there will be an increase in thyroid vascularity, thus will increase the resistance of the arterial bed and leading to an increase in peak systolic velocity of the thyroid artery. These are observed in the former study that we discussed earlier.

Compliance of the vessels is defined as the ability of the vessel to distend for a given change in pressure of the vessels (Glasser *et al.*, 1997). Atherosclerosis is a known causing factor that will reduce the vessels compliance thus will increase in peak systolic velocity value. If the atherosclerotic plaque is thick enough, causing narrowing and increased resistance of the arterial lumen will further influence the value of peak systolic velocity. Atherosclerotic plaque is easily identified on ultrasound as an echogenic lesion

in the arterial wall if it is present. The superior thyroid artery is a branch of the external carotid artery; thus, any pressure or flow velocity changes in the external carotid artery and the common carotid artery will influence the pressure and flow rate in the superior thyroid artery (Wu, 2009).

Widely known risk factors for atherosclerotic plaque development are hypertension, hyperlipidaemia, diabetes mellitus and smoking. However, since hyperthyroid disease influences heart rate and cardiac output, it will cause alteration in blood pressure; it is challenging to exclude all patients with underlying hypertension. As for our study, we will be screening the common carotid artery and external carotid artery during the sonographic examination. Patients with visible atherosclerotic plaque will be excluded from the study.

For the past few years, numerous studies have used peak systolic velocity of the thyroid artery or technetium pertechnetate in differentiating the causes of thyrotoxicosis. Some studies used peak systolic velocity or technetium pertechnetate in predicting relapsed after oral antithyroid therapy or RAI therapy. However, there is a lack of literature that correlates findings of technetium pertechnetate and sonographic findings of the thyroid gland for treating hyperthyroidism. Although TcTU is considered to have a low radiation dose compared to the iodine study, it still contributes extra radiation to the patient. Based on ALARA (As Low As Reasonably Achievable) principle, if we can offer less radiation or non-radiation study that give the same information as the radiation study without compromising the detail, it would be better for the patient.

2.6 Rationale of the study

This study is conducted to determine whether findings of pre-treatment RAI ultrasound of thyroid gland correlate with the value of technetium pertechnetate thyroid scan. This study will focus on all patients diagnosed with hyperthyroidism disease undergoing their first RAI treatment. Ideally, all patients subjected to radioactive iodine therapy should do the thyroid uptake scan either by technetium pertechnetate or I-131. This is to facilitate the nuclear medicine physician for iodine dose calculation so that each patient receives the appropriate dose for adequate ablation. However, due to its limited availability, time-consuming, costly, added to extra radiation dose and can be influenced by iodine-containing diet and medication for I-131, the thyroid uptake study is occasionally done, and the empirical fixed dose was given. Most patients are given the empirical fixed dose, which may not receive the appropriate dose for adequate ablation. Assuming the hypothesis is significant, and as an easily accessible, cheap, and non-radiation study, we can suggest implementing the ultrasound doppler study of the thyroid gland as a preliminary study in assisting the physician in calculating the RAI dose.

2.7 Conceptual framework

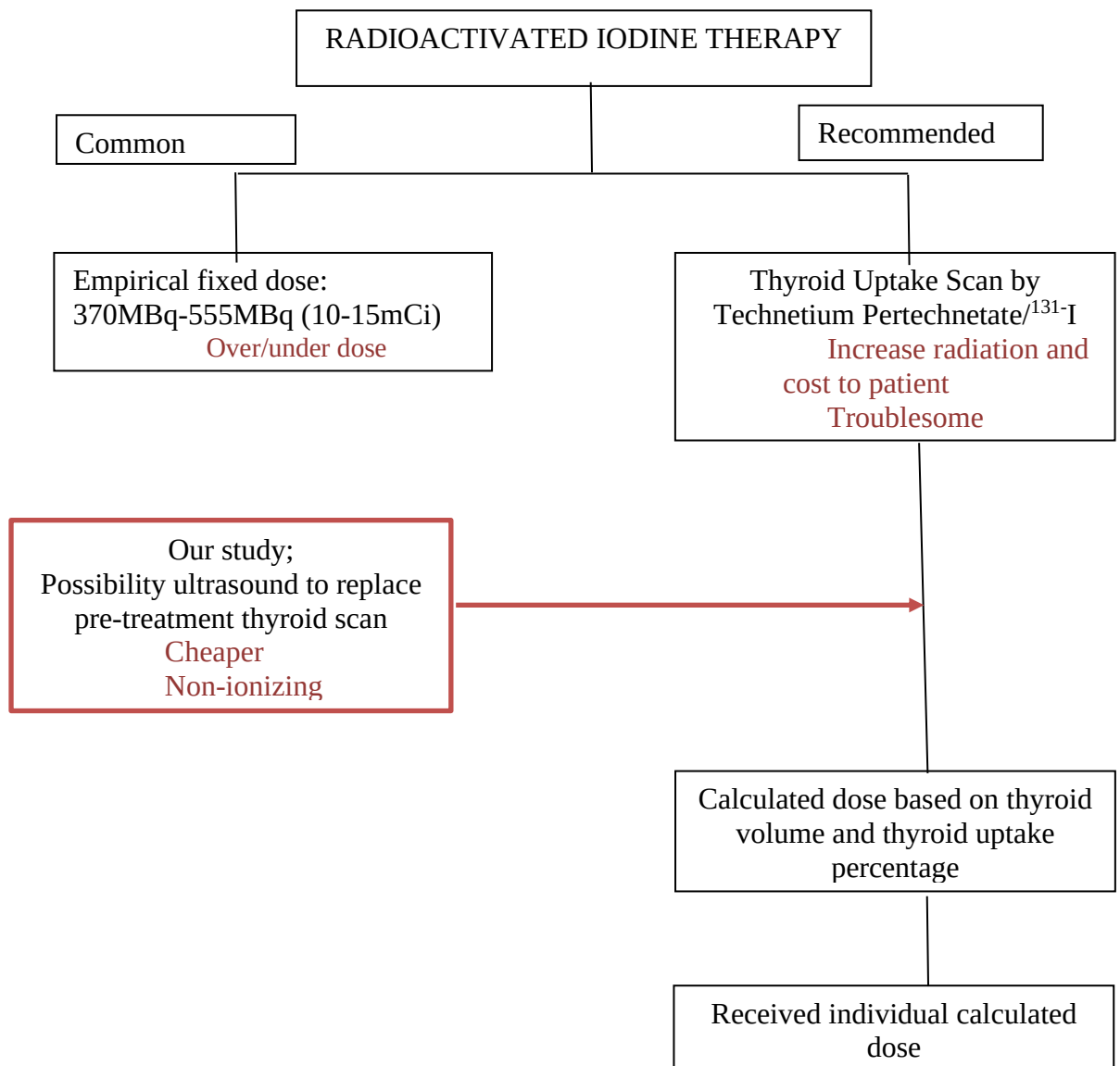


Figure 1: Conceptual framework flow of hyperthyroid treatment

CHAPTER 3: METHODOLOGY

3.1 Study design

This is a prospective cross-sectional study, and data will be collected in Nuclear Medicine in Hospital Universiti Sains Malaysia (Hospital USM) from June 2020 until October 2021.

3.2 Study location and duration

The study will be conducted in Hospital Universiti Sains Malaysia (Hospital USM) from June 2020 until October 2021.

3.3 Study population and sample

All primary hyperthyroid patients from Nuclear Medicine Clinic Hospital USM underwent their first RAI treatment.

3.4 Sampling technique

No sampling method was applied. All eligible patients that fulfilled the inclusion criteria were included in the study.

3.5 Inclusion criteria

1. Primary hyperthyroid patients that planned for first RAI
2. Age above 18 years old

3.6 Exclusion criteria

1. Patient with history of previous vascular neck injury
2. Previous history of hemithyroidectomy
3. Patient with a visible atherosclerotic plaque on ultrasound study

3.7 Sample size calculation

The sample size for objectives 1 and 2 were calculated using the estimation of the single mean formula, corrected to finite population number using Sample Size Calculator v4.0, prepared by Dr Najib, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia(Najib, 2015).

For objective 1, the sample size was calculated based on a previous study (Vita et al., 2019 and Zhao et al., 2012). The sample size for objective two was calculated based on an earlier study (Hou et al., 2015). Both objectives were calculated based on a corrected population of 137 patients who received RAI treatment last year, a precision of 0.05, a confidence level of 95%, and an anticipated dropout rate of 10%. Objective one was divided into volume and peak systolic velocity; the calculated sample size was 29 subjects for volume and 80 subjects for velocity. Objective 2 was divided into volume and Tc uptake; the calculated sample size was 14 subjects for volume and 12 subjects for uptake.

The sample size for objectives 3 and 4 was calculated using Pearson's correlation formula using Sample Size Calculator v2.0, prepared by Dr Wan Nor Ariffin, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia(Ariffin, 2019).

Objective 3 was calculated based on a previous study (Dong et al., 2019), while objective four was calculated on an earlier study (Malik et al., 2019). Both objectives were calculated with a power of 80%, an expected correlation of 0.9 for objective 3 and 0.7 for objective 4, a confidence level of 95% and an anticipated dropout rate of 10%. The calculated sample size was 8 subjects for objective 3 and 15 subjects for objective 4.

From all the sample size calculations, the largest sample size obtained was for Objective 1. Therefore, the total number of patients needed to be recruited in this study

was 80 patients. No sampling method was applied as we will take all hyperthyroid patients from nuclear medicine clinic Hospital USM who underwent their first RAI treatment. All patients that meet the study criteria will be included.

3.8 Research tools

1. Ultrasound Mindray (Mindray, Mindray Global, China) DC-8 Expert SN QH-76001072, L14-6we Transducer 3.5-16MHz
2. SPECT/CT GE DISCOVERY (GE SPECT/CT DISCOVER NM670, GE Healthcare, New York, United States) NM/CT 670 PRO
3. Picture Archive Communication System (PACS) in HUSM (PACS Universal Viewer Version 5.0 SP6)

3.9 Variable definition

Technetium-99m Pertechnetate thyroid uptake: The colour uptake of technetium by the thyroid gland is segmented using CT images using the software. The region of interest was manually drawn slice by slice from the tips of the upper pole to the tip of the lower pole of the thyroid gland on transaxial CT images. It is calculated using standard software (GE XELERIS (thyroid uptake) software).

Peak systolic velocity of the thyroid: Maximum systolic velocity measured within superior thyroid artery. The superior thyroid artery is identified as the first branch of the external carotid artery. The crossing point of the superior thyroid artery and the edge of the thyroid lobe is set as the positioning site. The insonation angle is maintained 0° - 60° and the angle of correction is adjusted so that it is parallel to the direction of blood flow.

Primary hyperthyroidism: Patient with an increase of thyroid hormone caused by thyroid gland malfunctioning.

3.10 Data collection

Patient cohort:

Subjects scheduled for first RAI treatment from June 2020 till October 2021 were recruited into the study based on inclusion and exclusion criteria. Informed consent was taken from the participants

Imaging data:

The selection of patients is identified from the nuclear medicine clinic who are hyperthyroid patients and subjected to RAI treatment for the first time. Written consent is obtained. All patients will undergo neck ultrasound before technetium study. As per the standard protocol of the technetium uptake study, all patients undergoing technetium study will be stopped their oral antithyroid medication five days before the examination. They will be subjected to low dose neck computed tomography (CT) for volume calculation after SPECT study on the examination day.

Ultrasound used ultrasound machine (Mindray DC-8 Expert SN, Mindray Global, China) using linear probe 3.5-16MHz, the patient is positioned supine with the neck is in the extended position. All patients are scanned longitudinally and transversely using B-mode US and colour Doppler for each thyroid lobe by the same operator at the same time. All patients will be screened for atherosclerotic plaque, and those with visible atherosclerotic plaque will be excluded—image from B-mode ultrasound, with maximum mediolateral, anteroposterior and craniocaudal measurement taken. Volume is calculated for each lobe using the formula for the ellipsoid model i.e., mediolateral length x anteroposterior length and craniocaudal length x 0.52 (Figure 2&3). Three measurements will be taken for the calculation of the mean value.

The colour flow imaging shows a red and blue spot in which the red spot indicated the direction of flow towards the transducer, and the blue spot indicated flow away from

the transducer. The superior thyroid artery is identified as the first branch of the external carotid artery. The crossing point of the superior thyroid artery and the edge of the thyroid lobe is set as the positioning site described in Zhao et al., (2012) (Figure 4). The insonation angle is maintained 0° - 60° , and the angle of correction is adjusted so that it is parallel to the direction of blood flow (Figure 5). The samples are taken triplicates for each lobe and expressed in the mean value.

The patient is subjected to a Technetium pertechnetate study on the same day as ultrasound. A five mCi technetium pertechnetate is injected intravenously. Pre-injection and post-injection syringe counts were acquired for 1 minute. Planar images are acquired 20 minutes after the injection using a single-photon emission computed tomography scintillation gamma camera (GE SPECT/CT DISCOVER NM670, GE Healthcare, New York, United States) equipped with low energy high resolution and parallel collimator with energy peak at 140keV and 20% energy window. Scanning is done in the supine position with the neck in an extended position pillow supporting the shoulder. After the planar image of the anterior neck is taken, the patient is then subjected to single positron emission computed tomography (SPECT) for 3-D images and SPECT-CT for volume calculation. The counts in the thyroid gland are determined by the region of interest (ROI) drawn along the border of the gland then subtracted with another ROI drawn just below the thyroid as background counts. After the ROI drawn, the percentage of TcTU is generated using standard software (GE XELERIS (thyroid uptake)) (Figure 6&7). As for volume calculation, the thyroid is segmented using CT images using the software and regions of interest (ROI) are manually drawn slice by slice from the tips of the upper pole to the tip of the lower pole of the thyroid on transaxial CT images. Volume is generated by the volumetric software (GE XELERIS (thyroid uptake)) to calculate the standardize uptake value (SUV) reflect as total volume of thyroid gland (Figure 8&9).

Information and data will be collected and documented in the datasheet, with patients' and subjects' information labelled with serial numbers to maintain privacy and confidentiality of subjects. The investigator will calculate the data obtained and then validate it by the Radiologist.

Demographic data:

Demographic data will be collected, including age, and gender.

3.11 Image analysis

Ultrasound of thyroid was performed using ultrasound machine (Mindray, Mindray Global, Shenzhen, China), and images were reviewed picture archive communication system. For the technetium pertechnetate study, scanning was done using a single-photon emission computed tomography scintillation gamma camera, (GE SPECT/CT DISCOVER NM670, GE Healthcare, New York, United States). GE XELERIS (thyroid uptake) software was used to calculate the volume and percentage of thyroid uptake.

3.12 Statistical analysis

Data were entered and analyzed using SPSS version 26. Demographic data was then analyzed using descriptively with frequency and percentage. Objectives 1 and 2 were described using descriptive analysis, and the result was reported using mean and standard deviation. Spearman correlation was used for objectives 3 and 4 because the data are not normally distributed.

3.13 Confidentiality and privacy

All subjects were identified by serial number, and the available data were kept anonymous. The SPSS data were stored in a password-protected computer, which researchers can only access. All the data were stored in CDs upon completion of the study. The databases on the computer were erased once completed research. The results were presented as grouped data, and thus it would not reveal any individual identity of the patients. The researchers retained the data for knowledge purposes only. Neither the name nor any identifying information was used in any publication or presentation resulting from this study.

3.14 Ethical consideration

The study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM code: USM/JEPeM/20010037) and complied with the Declaration of Helsinki (see APPENDIX B).

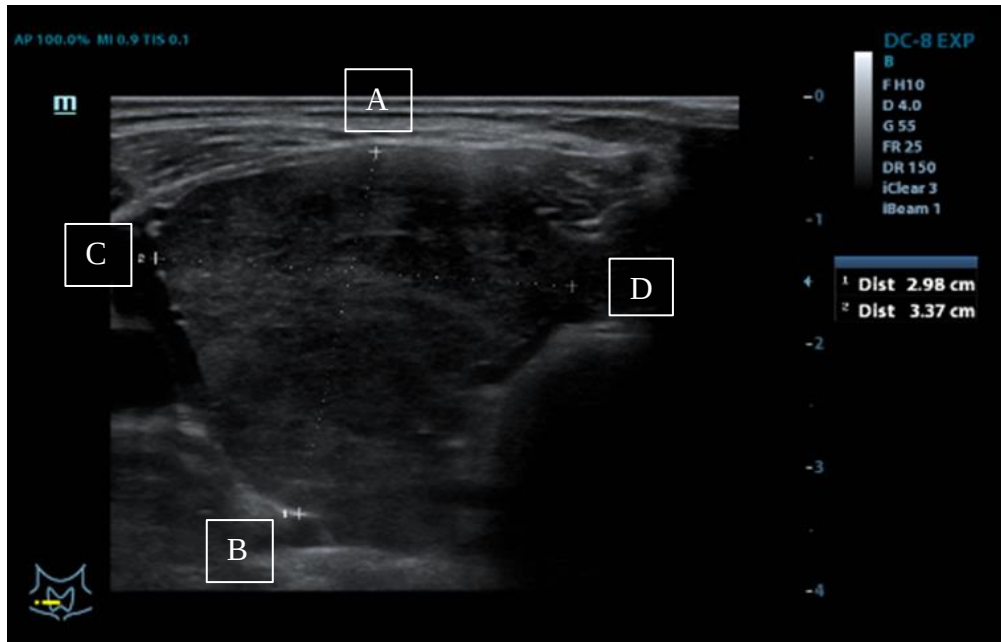


Figure 2: Ultrasound Image: Maximum anteroposterior (AP) was measured from point A to B and mediolateral (ML) measured from point C to D.

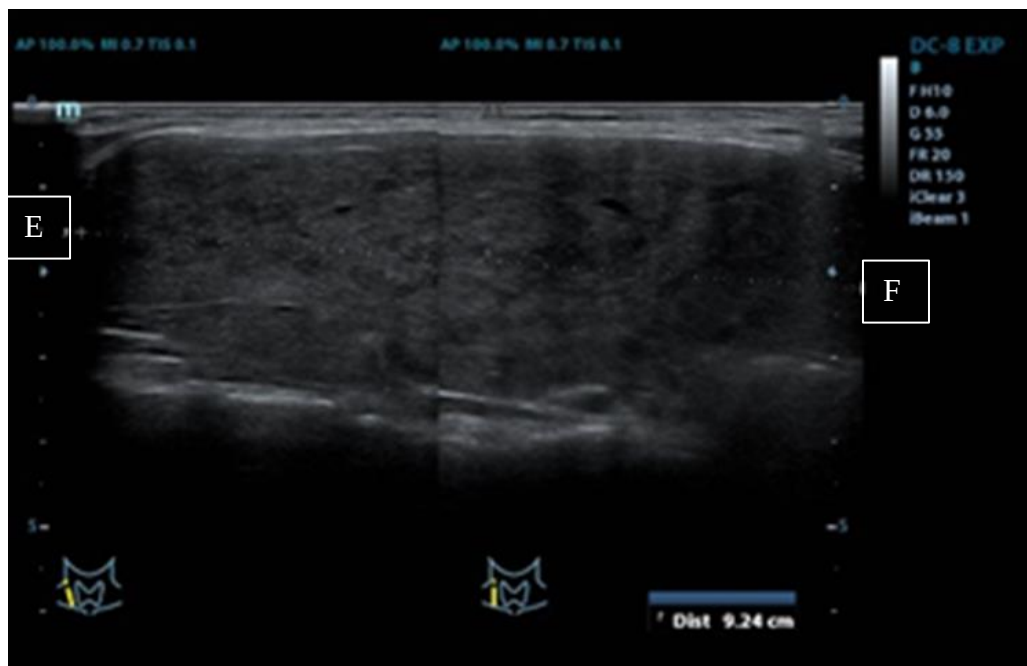


Figure 3: Ultrasound image: Maximum craniocaudal was measured from point E and F.