DOSE DETERMINATION OF RADIOACTIVE IODINE IN TREATMENT OF HYPERTHYROIDISM UTILIZING QUANTITATIVE 99MTC-PERTECHNETATE THYROID SPECT/CT

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Abstract
The aim is to evaluate the usefulness of technetium pertechnetate (^{99m}Tc) thyroid uptake (TcTU) obtained from thyroid scintigraphy using quantitative Single Photon Emission Computed Tomography / Computed Tomography (SPECT/CT) in determining personalised dose of ^{131}I radioactive iodine (RAI) therapy for hyperthyroidism. A study of 131 participants with hyperthyroidism referred for RAI therapy was performed. 66 participants were enrolled into the prospective (calculated dose) group whereas 65 participants were from retrospective control (fixed dose) group. Quantitative thyroid SPECT/CT was performed for the prospective group prior to receiving RAI. TcTU and thyroid gland volume obtained from the Quantitative thyroid SPECT/CT were incorporated into modified Marinelli formula for RAI dose. Outcome of RAI was determined at the end of 6 months follow-up. Descriptive analysis of demographics and regression analyses of variables were performed. Mean calculated RAI dose was 17.74 mCi (SD 6.27) with mean dose for successful RAI at 6 months was 16.42 mCi (SD 5.87). Success rate was 80.3 % in the calculated group, versus 60.0 % in the fixed dose group (p-value 0.013). Regression analysis showed thyroid gland volume as an independent factor in determining successful outcome (adjusted OR = 0.963 CI: 0.942, 0.985) with volume of <77.2 ml more likely to produce successful outcome; sensitivity and specificity of 69 % and 83 % respectively. Quantitative SPECT/CT is useful in determining personalised dose of ^{131}I RAI therapy. It significantly improves treatment outcome for hyperthyroidism as compared to the conventional fixed dose method.

Keywords: Radioactive iodine therapy, Hyperthyroidism, SPECT/CT, Technetium Thyroid Uptake

Introduction

Hyperthyroidism is a common endocrine disorder with a prevalence of 0.2-1.3 % (1). Various aetiologies contributed to hyperthyroidism with the commonest being Graves' disease, toxic multinodular goitre (TMNG) and toxic adenoma (TA). The diagnosis of hyperthyroidism is usually made based on clinical symptoms and biochemical profile suggestive of hyperthyroidism. Imaging techniques such as ultrasonography examination of the neck and thyroid scintigraphy are complimentary investigations used to further evaluate the disease by identifying and characterising thyroid nodules as well as describing the anatomy of thyroid gland.

Initial treatment usually involved the utilisation of anti-thyroid drugs; methimazole or propylthiouracil and has been shown to lead to remission of Graves' disease in approximately 60 % of cases with variation reported among studies involving the European and Japanese population (2, 3). However, definite therapy with radioactive iodine (RAI) therapy and surgery is recommended in resistant and relapsed cases. Various methods of RAI dose determination have been in practice namely fixed, empirical and calculated dose. However, no single method has been shown to be conclusively superior to the other. However, the calculated dose of RAI offers advantageous over fixed dose with multiple studies stating success rate ranging from 80 % to 93 % (4).

Traditionally, calculation of RAI dose is done by utilising the Marinelli's formula, first described by Marinelli in 1948 which considers thyroid gland volume, desired absorbed dose to the gland, percentage (%) of thyroidal uptake and effective half-life (Teff) of RAI (5). Currently, this is the recommended formula and is the basis for dosimetry approach in the management of hyperthyroidism (6). Iodine-123 (123I) and Iodine-131 (131I) are used extensively in determining the percentage of thyroidal uptake and residence time by performing the 4- and 24-hours radioactive iodine uptake (RAIU) study. Iodine compound radiopharmaceutical such as 123I and 131I is the preferred radiopharmaceutical because it allows the evaluation of thyroidal uptake, iodine organification and thyroid hormone metabolism hence ensuring complete assessment of thyroid gland function. 123I is the ideal radiopharmaceutical for imaging and uptake measurement of thyroid gland because it has superior image quality and lower radiation exposure than 131I in addition to shorter overall procedure length. However, 123I is expensive and is not readily available hence Technetium-Tc99m pertechnetate (99mTcO4) has been explored and touted to be a suitable substitute in determining percentage thyroidal uptake. 99mTcO4 possesses similar characteristics to iodine but with better imaging qualities such as shorter uptake imaging time (20 minutes vs 24 hours), better image resolution, no beta radiation and lower overall radiation dose to the patient. Furthermore, Smith has proposed an equation to convert the percentage of 99mTcO4 thyroid uptake (TcTU) to RAIU hence allowing the incorporation of TcTU to the existing Marinelli's formula as eloquently described by Szumowski (7, 8).

The advent of hybrid imaging such as single photon emission tomography / computed tomography (SPECT/CT) is advantageous and is able to quantitatively estimate the TcTU and RAIU equivalent in thyroid gland using 99mTcO4 thyroid scintigraphy with good correlation to the conventional RAIU measurement obtained via gamma probe (9-11). Moreover, the utilisation of SPECT/CT has proved to be excellent in determining anatomical parameters such as volume measurement, an important parameter for dose calculation (9, 11).

The utilisation of fixed-dose RAI therapy has always been the preferred method for RAI therapy in most centres in Malaysia due to its simplicity, dispensing ease and proven efficacy. However, the lack of personalisation in terms of treatment as well as the risk of over or undertreating a patient has never been truly explored. In addition, due to the heterogeneity of demographics even among Malaysian population (east coast versus west coast and urban versus rural), it has been found that response to the standard and commonly practice fixed dose of 15 mCi may not be the best dose to suit all population especially among patients with hyperthyroidism in east coast states of Malaysia whereby the failure rate of single fixed dose RAI was much higher than those reported in the west coast states; 47.5 % versus 40 % (4, 12, 13). Moreover, the apparent difference in dose of RAI used between centres in Malaysia and elsewhere in the Asia-Pacific region suggested other factors could have contributed to treatment success and failure, with the thyroid gland volume consistently being cited to significantly affect treatment outcome. For these reasons, a prospective study was carried out in our centre to ascertain the usefulness and effectiveness of using TcTU-based Marinelli's formula in determining the dose of RAI in the treatment of hyperthyroidism against the standard practice of fixed-dose RAI therapy. The modified Marinelli's formula proposed by Szumowski incorporating the correlation equation formula proposed by Smith will be adopted (7, 8). Moreover, this study was also meant to explore the feasibility and convenience of conducting dosimetry for RAI therapy in treatment of hyperthyroidism utilising quantitative SPECT/CT. In addition, this study aims at identifying factors influencing treatment outcome particularly among our patient demographics as well as assessing possible predictive factors in obtaining successful outcome of treatment.

Materials and Methods

This was a prospective against historical cohort study of fairly equal distribution. 66 patients with hyperthyroidism consisting of Graves' disease and toxic multinodular goitre referred for RAI therapy were recruited and followed-up for 6 consecutive months. On the other hand, data from

65 patients whom received fixed dose RAI were recorded, analysed and included in the historical cohort group labelled as fixed dose group. The outcome of RAI therapy either by fixed or calculated dose was determined at the end of 6 months. This study was conducted in Nuclear Medicine Clinic, Department of Nuclear Medicine, Radiotherapy and Oncology, Hospital Universiti Sains Malaysia from April 2018 to October 2019.

Subject recruitment

The inclusion criteria included consenting adult, age ≥18-year-old with biochemically proven hyperthyroidism which was defined as 1) Serum Thyroid Stimulating Hormone (TSH): <0.2 mIU/L and/or 2) Serum Thyroxine (Free T4): ≥22 pmol/L.

Patients with hyperthyroidism caused by ectopic thyroid tissue, history of previous thyroid surgery, features suspicious of malignancy on ultrasonography examination of the neck (TI-RADS >3) and cytology or biopsy-proven thyroid malignancy were excluded from the study.

Thyroid scintigraphy (planar & SPECT/CT) for determination of TcTU

Patients who fulfilled the inclusion criteria were scheduled for 99mTcO4- thyroid planar scintigraphy and SPECT/CT acquisition of the neck. Patients were required to withhold anti-thyroid medications (methimazole or propylthiouracil) and to be on low iodine, nil-seafood diet for 1 week prior to thyroid scintigraphy. Clinical assessment and symptoms review were conducted and serum TSH and free T4 were sampled and measured. 99mTcO4- thyroid planar scintigraphy with SPECT/CT acquisition of the neck was performed using GE Discovery NM/CT 670 Pro gamma camera.

Thyroid scintigraphy was performed utilising a dose of ±5 mCi of 99mTcO4- which was prepared by in-house radio-pharmacist and the actual dose in MBq or mCi was determined by dose calibrator Biodex AtomlabTM 500 (New York, USA). The syringe containing the predetermined dose of 99mTcO4- was imaged for 1 minute to obtain the pre-injection count. 99mTcO4- of ±5 mCi was then injected to participants via an in-situ venous catheter. The empty syringe was then imaged for 1 minute to determine post-injection count and it was also measured using the dose calibrator to determine the residual activity of 99mTcO4- in the syringe. The injection site on the participant's hand was imaged for 1 minute to determine the injection site count. Planar images of the anterior neck followed by SPECT/CT acquisition of the neck were performed after 20-minutes injection of 99mTcO4- with the participant in a supine position, neck slightly extended and head supported by a pillow placed under the shoulder. Planar image of the anterior neck was acquired for 1-minute duration using a low energy high resolution (LEHR) detector with parallel hole collimator with energy peak set at 140 keV, ±20% energy window, matrix size of 256x256 and zoom of 2.5. On the other hand, SPECT/CT acquisition of the neck was done with the following parameters: matrix size 128x128, 15-seconds per stop, 6o angular motion (180o rotation per detector, 360o total rotation). CT parameters were as follow; helical slice thickness 2.5mm, interval 2.5mm, pitch 1.375:1, rotation speed 27.5 mm/rotation, rotation time 0.7s, 120kVp and 30-100 mA. No contrast agent was used for this study.

Quantitative SPECT/CT

Quantitative SPECT/CT method was used to determine the percentage TcTU. The build-in software by GE Healthcare, XelerisTM Functional Imaging System specifically Q.Metrix was utilised. Calibration factor of the SPECT/CT scanner with a system sensitivity of 176.18 cnt/min/uCi was determined from previous phantom and sensitivity studies conducted by the resident medical physicist.

The thyroid gland was then segmented using the non-contrasted CT images on the software and regions of interest (ROIs) were manually drawn slice by slice from the upper tips to the lower poles of the thyroid gland on the trans-axial CT images. ROIs were also reflected on SPECT and SPECT/CT images. Volume of interest (VOI) was generated to include the whole thyroid gland. In addition, other parameters such as thyroid gland volume, maximum and mean standardised uptake values were also obtained via the quantitative SPECT/CT analysis (Figure 1).

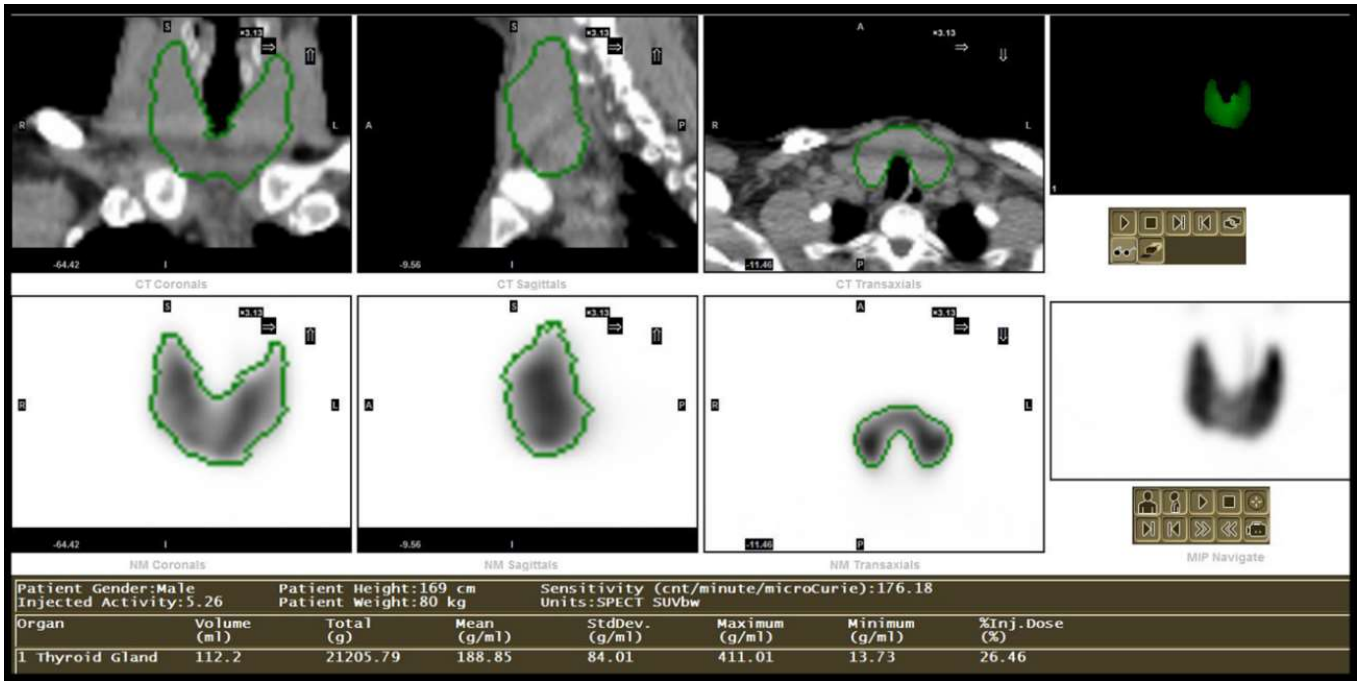

Figure 1: Thyroid Scintigraphy with Quantitative SPECT/CT parameters

The TcTU was calculated automatically by the software, utilising the following formula:

TcTU = (Counts over thyroid gland - Counts over background)/(Counts of injected activity) x 100

RAI dose calculation

RAI dose calculation was done by utilizing the modified Marinelli's formula proposed by Szumowski et al. (1996) and incorporating the TcTU to RAIU formula proposed by Smith et al. (1990). The determination of the administered activity of A in MBq was derived from utilising the proposed formulas follows;

A (MBq) = (25 x vol (ml) x D (Gy))/([17.72 x ln(TcTU) + 30.4] x 5.5)

where Vol (ml), D (Gy) and TcTU are thyroid volume in ml, absorbed dose to thyroid gland in Gray (Gy) and percentage technetium thyroid uptake at 20mins (%) respectively. A (MBq) is Administered dose in megabecquerel, MBq.

Follow-up and outcome determination

Patients in the prospective group were followed-up for 6 consecutive months. During the follow-up period, clinical assessment, symptoms review, and biochemical assessment were carried out and recorded. Similar parameters for a similar period of 6-months were also recorded for the historical cohort group. Patients achieving biochemical euthyroid or hypothyroid status were considered a successful outcome, whereas patients with biochemical hyperthyroid status (persistent or relapsed) at 6-months were considered failed outcome. The normal range of serum TSH and T4 were 0.270-4.20 mIU/L and 12.0-22.0 pmol/L respectively.

Statistical analysis

Statistical analyses were performed using SPSS IBM software for Mac version 24.0 (IBM, NY, USA). Demographics of the patients were summarised using descriptive studies with statistical outcome expressed in frequency (percentage, %) min, max, mean, and standard deviation for normal data or median and interquartile range (IQR) for skewed data. The relationship between mean dose required for hyperthyroidism patients and the treatment response was analysed using an independent t-test. The relationship between TcTU with the treatment outcome was analysed using simple logistic regression test. A comparison between two groups was performed using Chi-square test with Fisher Exact's correction when appropriate. For unpaired data, the differences in distribution between the two groups were analysed by independent t-test or Mann-Whitney test according to normal or skewed distribution of the data. P value of 0.05 and less ($p < 0.05$) was considered as significant.

Results

Table 1 shows the demographic data for the overall subjects for this study. The study population consists of 2 fairly equal groups; retrospective cohort (fixed-dose) group and prospective (calculated-dose) group. The control group consists of 65 participants and the prospective group consists of 66 participants. The mean age of the study population consisting of both groups (n=131) was 44.88-year-old with the youngest age of 18-year-old, and the oldest age of 75.3-year-old. The mean age for male and female were 45.03-year-old and 44.83-year-old respectively. The study population was predominantly female (n=100) with ratio of female-to-male was 3.23. Malay ethnicity dominated the study population, 91.6% which was consistent with the overall

demographics of the study location. Graves' disease accounted for the majority of cases of hyperthyroidism referred for RAI therapy, amounting to 59.5 %. Toxic MNG on the other hand was the second most common cause of hyperthyroidism, totalling 26.7 %. The distribution of hyperthyroid aetiologies was similar for both groups with Graves' disease being the most common, 55.5 % in the retrospective (fixed-dose) group, and 63.6 % in the prospective (calculated-dose) group. The diagnosis of Graves' disease was made by the positive detection of TRAb as documented by primary referring physicians where else diagnosis of toxic MNG was made based on radiological appearance with the presence of multi-nodular thyroid gland on USG. A total of 18 patients (13.7 %) with hyperthyroidism referred for RAI had no definite diagnosis, hence for the purpose of this study, termed unspecified. For the prospective group (n=66), further characterisation of study population was carried out and the findings were summarised in Table 2.

Tables 1: Demographics of study population (n=131)

Variables	Study Population (n=131)	
	Mean (SD)	**n (%)**
Age	44.88 (12.40)	
Gender		
Male		31 (23.7)
Female		100 (76.3)
Ethnicity		
Malay		120 (91.6)
Chinese		8 (6.1)
Others		3 (2.3)
Diagnosis		
Graves' Disease		78 (59.5)
Toxic Multinodular Goitre		35 (26.7)
Hyperthyroidism, Unspecified		18 (13.7)

Table 2: Clinical characteristics of the participant of the prospective (calculated-dose) group

Variables	Study Population (n=66)	
	Mean (SD)	**Median (IQR)**
Patient's anthropometry		
1. Weight (kg)		65.5 (53.4, 74.0)
1. Height (m)	1.58 (0.08)	
2. BMI (kg/m^2)		25.10 (22.1, 29.1)
Duration of Disease (months)		60.00 (36.0, 120.0)
Goitre size (WHO classification)		**n (%)**
- Grade 0: Non-palpable		11 (16.7)
- Grade 1: Palpable		23 (34.8)
- Grade 2: Visible		32 (48.5)
Fine tremors		27 (40.9)
Thyroid eye sign		12 (18.2)
Symptoms at initial diagnosis		
- Palpitation		63 (95.5)
- Excessive sweating		58 (87.9)
- Heat intolerance		56 (84.8)
- Fine tremors		55 (83.3)
- Unintentional loss of weight		51 (77.3)
- Irritability		46 (69.7)
- Insomnia		25 (37.9)
- Diarrhoea		13 (19.7)
Complications of hyperthyroidism		34 (51.5)
- Thyroid associated ophthalmopathy		12 (18.2)
- Cardiac arrhythmias		11 (16.7)
- Thyroid storm		6 (9.1)

- Thyroid cardiomyopathy	6 (9.1)
- Hypokalaemia periodic paralysis	4 (6.1)
- Recurrent miscarriages	2 (3.0)
Treatment – Anti-Thyroid Drugs	
- Carbimazole	65 (98.5)
- Propylthiouracil	1 (1.5)
- Propranolol	34 (51.5)
Dose of Anti-Thyroid Drugs	
- Carbimazole (mg)	10.00 (5.0, 15.0)*
Biochemical Profile	
- Free T4 (pmol/L)	21.4 (16.1, 42.4)*
- TSH (mIU/L)	0.04(0.005,0.850)*

Free T4=Tetraiodothyroxine (Normal: 12-22 pmol/L), TSH=Thyroid Stimulating Hormones (Normal: 0.24-6.40 mIU/L).
** Median (IQR: Inter-quartile range).*

The quantitative SPECT/CT analysis yielded several parameters as tabulated in Table 3. The mean thyroid gland volume was 62.75 ml (SD 34.08). The TcTU at 20 minutes had a median of 14.68 % (IQR: 7.8, 23.1) where else the estimated RAIU at 24 hours had a mean of 76.57 % (SD: 13.10).

Table 3: ^{99m}Tc-pertechnetate quantitative thyroid SPECT/CT findings and mean calculated dose

Variables	Study Population (n=66)	
	Mean (SD)	Median (IQR)
Thyroid gland volume (ml)	62.75 (34.08)	
SUVmean	310.12 (1033.31)	
SUVmax	487.62 (228.81)	
TcTU SPECT/CT (%)		14.68 (7.8, 23.1)
Estimated RAIU (%)	76.57 (13.10)	
Calculated dose of RAI (mCi)	17.74 (6.27)	

TcTU(%) = percentage 20-minutes Technetium Thyroid Uptake (Normal: 0.24 – 3.34), RAIU(%) = percentage 24-hour Radioiodine Thyroid Uptake, mCi = milli-Curie.

At 6-months follow-up, an impressive 53 patients in the prospective calculated-dose group achieved successful treatment outcome, consisting of 31 patients with hypothyroid status and 22 patients achieved euthyroid status which accounted for 47 % and 33.3 % respectively. Interestingly, during the course of 6 months follow-up, 7 participants achieved either euthyroid or hypothyroid status at 3 months follow-up but subsequently had recurrent of hyperthyroid at 6 months follow-up (Table 4). In comparison to the retrospective group with fixed dose of RAI, there was statistically significant difference between successful outcome at 6 months post RAI; fixed dose (n=39, 60 %) and calculated dose (n=53, 80.5%), p-value 0.013 (Table 5).

Table 4: Further breakdown of the outcome at 6 months post RAI therapy (n=66)

Outcome 6-months post RAI	n	%
Fail: Hyperthyroid	13	19.7
Persistent Hyperthyroid *(Hyperthyroid at 3-months and 6-months follow-up)*	6	9.1
Recurrent Hyperthyroid *(Hypothyroid at 3-months but hyperthyroid at 6-months follow-up)*	7	10.6
Successful: Hypothyroid or Euthyroid	53	80.3
Hypothyroid	31	47.0
Euthyroid	22	33.3

Table 5: Outcome at 6 months post RAI therapy between fixed and calculated dose method

	Outcome 6 months post RAI			
	Fail - Hyperthyroid	Successful – Hypo- Or Euthyroid	Total	*p*-value
	n (%)	n (%)		
Fixed	26 (40.0)	39 (60.0)	65	0.013*
Calculated	13 (19.7)	53 (80.3)	66	

**Fisher's Exact test as 0% of cells have expected count less than 5.*

The mean calculated dose of RAI utilising the modified Marinelli's formula incorporating the quantitative SPECT/CT-derived TcTU was 17.74 mCi (SD 6.27). Patients who achieved successful outcome required a mean dose 16.42 mCi (SD 5.87) whereas patients who had failed to become euthyroid or hypothyroid at 6-months had a mean dose RAI of 23.15 mCi (SD 4.86). This was also consistent with thyroid gland volume whereby larger thyroid gland volume contributed to higher failure rate in achieving a successful outcome; mean volume of 96.92 ml vs 54.36 ml respectively. These results indicated that larger volume of thyroid gland would lead to higher RAI dose and consequently higher number of treatment failure. Interestingly, higher percentage RAIU however did not translate to success of RAI therapy despite conventional belief as shown in Table 6.

Table 6: Factors determining successful treatment outcome in the prospective group

Variables	Mean (SD)		Mean difference (95% CI)	t-stat* (df)	*p*-value
	Failure	Success			
RAI Dose (mCi)	23.15 (4.86)	16.42 (5.87)	6.74 (1.76 – 3.21)	3.819 (64)	<0.005
Thyroid gland (ml)	96.91 (36.53)	54.36 (27.93)	42.55 (24.17 – 60.93)	4.634	<0.005
Estimated RAIU (%)	84.08 (13.08)	74.73 (12.55)	9.35 (1.53 – 17.17)	2.39 (64)	0.020

**Independent T-test*

Logistic Regression Analysis were performed to determine associated factors (variables) towards successful outcome at 6 months post RAI therapy. The findings of these analyses were tabulated in Table 7. Further multivariate regression analysis showed that the thyroid gland volume as the only significant factor influencing outcome at 6 months follow-up following administration of calculated-dose RAI (Table 8).

Table 7: Simple Logistic Regression on associated variables towards successful treatment outcome

Variables		Regression coefficient, b	OR (95%CI)	Wald (df)	*p* value
Patient Demographics					
Age		-0.018	0.982 (0.934, 1.033)	0.506 (1)	0.477
Gender	Female – Male	-0.246	0.782 (0.149, 4.097)	0.085 (1)	0.771
Ethnicity	Chinese – Malay	19.918			
	Others - Malay	19.918			
Height (cm)		1.967	7.151 (0.004, 13654)	0.261 (1)	0.610
Weight (kg)		0.025	1.025 (0.982, 1.071)	1.205 (1)	0.272
BMI (kg/m^2)		0.051	1.052 (0.936, 1.183)	0.724 (1)	0.395
Disease Characteristics					

Diagnosis	TMNG – GD	-0.194	0.824 (0.213, 3.183)	0.079 (1)	0.824
	Unspecified – GD	0.163	1.176 (0.120, 11.51)	0.020 (1)	0.889
Duration of Disease (months)		**-0.005**	**0.995 (0.986, 1.003)**	**1.417 (1)**	**0.234**
Goitre Size	Grade 1 - Grade 0	-0.405	0.667 (0.061, 7.254)	0.111 (1)	0.739
	Grade 2 – Grade 0	**-1.364**	**0.256 (0.028, 2.296)**	**1.484 (1)**	**0.223**
Serum T4 Pre-RAI (pmol/L)		-0.002	0.998 (0.971, 1.027)	0.015 (1)	0.903
Serum TSH Pre-RAI (mIU/L)		**1.568**	**4.796 (0.794, 28.99)**	**2.917 (1)**	**0.088**
Status Pre-RAI (toxic/non-toxic)		**-0.773**	**0.462 (0.126, 1.685)**	**1.369 (1)**	**0.242**
Quantitative Thyroid SPECT/CT					
Thyroid gland volume (ml)		**-0.038**	**0.963 (0.942, 0.985)**	**10.98 (1)**	**0.001**
TcTU SPECT/CT (%)		**-0.071**	**0.932 (0.885, 0.982)**	**7.066 (1)**	**0.008**
TcTU Planar (%)		**-0.074**	**0.929 (0.875, 0.987)**	**5.762 (1)**	**0.016**
SUVmean (g/ml)		0.000	1.000 (0.998, 1.003)	0.112 (1)	0.738
SUVmax (g/ml)		0.000	1.000 (0.997, 1.003)	0.011 (1)	0.916
Estimated RAIU (%)		**-0.067**	**0.935 (0.882, 0.992)**	**5.009 (1)**	**0.025**
RAI Dose (mCi)		**-0.191**	**0.826 (0.733, 0.931)**	**9.851 (1)**	**0.002**

**For both variables,*

***statistically significant p-value taken as <0.25 with variables fulfilling this criterion **bold.** The value of <0.25 was favoured over the traditional <0.05 as to ensure important identifying factors not missed (Bendel and Afifi, 1977).*

Table 8: Association between variables towards outcome with multivariable logistic regression analysis

Variables	Regression coefficient, b	Adjusted OR (95%CI)	Wald (df)	*p*-value
Thyroid gland volume	-0.0.38	0.963 (0.942, 0.985)	10.977 (1)	0.001

Receiver operator characteristics (ROC) curve analysis as in Figure 2 showed that the area under the curve (AUC) was 0.838 which is >0.7, (95 % CI: 0.73, 0.94) suggesting good model fit to the data. The overall analysis showed thyroid gland volume could be used to predict outcome of RAI therapy. Based on the ROC curve analysis, a thyroid gland volume with a threshold of 77.2 ml could predict outcome of RAI treatment with sensitivity and specificity of 69 % and 83 % respectively. This finding showed that RAI would likely be successful if administered to patient with thyroid volume of <77.2 ml. The final model also showed that 1.0 ml increased in thyroid volume decreased the odds of achieving successful outcome at 6-month post RAI by 0.963.

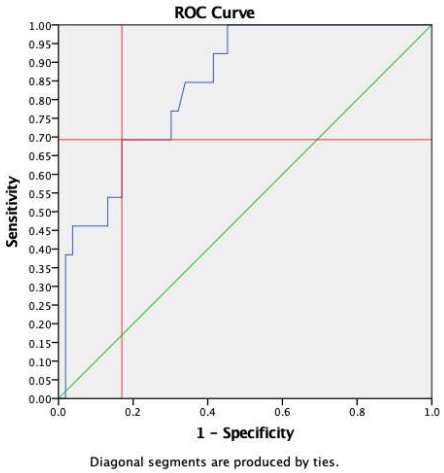

Figure 2: ROC curve analysis

Discussion

RAI is one of the definite treatments of hyperthyroidism especially in cases of persistent or relapsed hyperthyroidism post treatment with ATD. RAI is preferred over surgery as it is not invasive and well tolerated. RAI can be administered in several ways; fixed, empirical, or dosimetry-based calculated dose. However, to date, conflicting data were available regarding the superiority of these methods. Meta-analysis and systemic review by Rokni et al., (2014) examining 6 studies comparing calculated versus fixed dose showed successful therapy with calculated dose as compared to fixed dose with risk ratio of successful outcome of RAI of 1.17, favouring calculated dose and mean dose of 14.14 mCi but with lower risk of hypothyroidism [11]. An earlier systemic review and meta-analysis by de Rooij (2009) evaluating 8 studies comparing calculated versus fixed dose of RAI showed that both methods were equally effective in treating hyperthyroidism (14).

The mean calculated dose of RAI in this study was 17.74 mCi (SD 6.27) with mean calculated dose for successful outcome of 16.42 mCi (SD 5.87 mCi). This was higher compared to the fixed dose of 15 mCi in the retrospective group. Our mean dose was like those published by Wong which was 18.1 mCi producing a success rate of 93.3% (15). A systemic review by Rokni showed a calculated mean dose for successful treatment of hyperthyroidism of 14.14 mCi (11). Lee et al., (2018) however showed that the mean calculated dose was 22.0 mCi which was higher than our recorded value (4). Interestingly, despite the difference in mean dose for successful outcome, this study as well as in Lee et al., (2018) showed similar mean dose contributing to treatment failure which were 23.15 and 23.0 mCi respectively. Similarly, Wong et al., (2018) also stated higher mean dose (19.9 mCi) in the treatment failure group as compared to the success group (18.1 mCi) (15). Fascinatingly, a study by Howarth et al., (2001) showed a mere mean dose of 3.57 mCi was adequate to achieve successful outcome of either hypothyroid or euthyroid post RAI (16).

In this study and the study by Wong et al., (2018) treatment failure was more prevalent in participants with large goitre and higher TcTU as well as RAIU (15). Pertaining to the study by Howarth, volume was also a determining factor in achieving successful outcome of RAI but a point to note is in their study, the mean volume of their participants was significantly smaller compared to this study, 21.9 ml for responders versus 39.9 ml for non-responders hence explaining the significantly lower RAI dose prescribed (16).

This study also demonstrated that thyroid volume was a good predictor in predicting treatment outcome of RAI. A threshold of 77.2 ml was shown to have a sensitivity of 69 % with specificity of 83 %. Studies by Zantut-Wittmann et al., (2005), El-Kareem et al., (2014), Sfiligoj et al., (2015) and Yang et al., (2017) showed thyroid gland volume as an important independent variable in predicting response to RAI with odds ratio ranging from 3.31 to 0.99. However, the volume described in these studies varies significantly ranging from 22 to 62 ml (17-20). Our cut-off value of 77.2 ml was higher compared to the above-mentioned thyroid gland volumes, likely reflecting the high prevalence of endemic goitre among population in our study locality with a prevalence of 36.8% (13). It is worth noting that few patients had to be excluded from study population as these patients received doses less than the stipulated calculated dose from quantitative thyroid SPECT/CT. These patients were informed upfront of the likelihood of failure of single RAI dose prior to receiving their first RAI and interestingly, all the patients were unsuccessfully treated at 6-months follow-up (remained hyperthyroid requiring ATDs) and subsequently required repeat RAI. More intriguingly, all these patients had thyroid gland volume in excess of 100 ml and were initially counselled for surgery but opted not to proceed due to either personal preference or specific contraindications to surgery. This was in agreement to our determined cut-off value of 77.2 ml for successful treatment outcome. Moreover, the cut-off value based on our prediction model was similar to the value specified by American Thyroid Association in 2016 which recommended surgery for goitre larger than 80 ml which was further supported by the European Thyroid Association in 2018 which indicated favouring surgery against RAI in large goitre albeit no specific size was mentioned (3, 21).

In this study, participants in the prospective calculated dose cohort, 80.3 % (53/66) showed successful outcome in contrast to the retrospective control cohort where only 60 % (39/65) of participants achieved euthyroid or hypothyroid at 6 months post-RAI. This finding is almost similar to another local study conducted by Lee et al. (2018) where 82.1 % achieved euthyroid/hypothyroid at 6 months [4]. Other studies from the rest of the globe have also shown similar findings; Nwatsock et al. (2012) in France achieving 88.3 % and Schiavo et al. (2014) in Italy recording 81.7 % success rate of euthyroid or hypothyroid at 6 months post RAI (22, 23). A randomised study involving 40 patients in India, equally divided into the fixed and calculated dose group showed success rate of 65 % in calculated dose group versus 60 % in fixed dose group, but this finding was not statistically significant (24).

A retrospective study by Wong KK (2018) examining 316 patients who had received RAI based on calculated dose over a period of 9 years showed that 91 % of patients achieved either euthyroid or hypothyroid at 6 months post single dose of calculated RAI with an overall success rate of 93.3 % at 1 year. They reported the mean dose of calculated RAI dose was 18.1 ± 6.8 mCi with mean response time of 110.2 days which were fairly similar to this study's mean dose of 16.42 ± 5.87 mCi and mean response time of 140.2 days (15).

Further breakdown of the 53 participants of this study

who were treated successfully at 6 months revealed that 22 (33.3 %) of them were biochemically euthyroid and 31 (47.0 %) were hypothyroid. A study by Mohamed WMW. et al. analysing a pool of 137 patients who received RAI in our centre from the year 2002-2011 revealed the incidence of hypothyroidism at 1-year post RAI of 32.9 % (12). This was much lower than the recorded incidence of hypothyroidism in this study. A possible explanation to this is the lower dose of RAI prescribed in his study population whereby patients received dose of no more than 15 mCi. This factor was also evident in several other studies whereby higher dose led to higher rate of hypothyroidism (25, 28). However, although lower dose of RAI led to less incidence of hypothyroidism, it also led to higher incidence of treatment failure whereby 47.4% of patients remained hyperthyroid at 12-month post RAI (12). Nonetheless, similar incidence of hypothyroidism was also recorded in other studies, ranging from 51-57 % at 6 months post RAI (25, 26). The high incidence of hypothyroidism at 6 months post RAI as compared to the reported 32.9 % at 1-year post RAI may be due to transient hypothyroidism frequently seen during the course of post RAI (27).

An earlier retrospective study of hypothyroidism post RAI therapy conducted in our centre showed that gender played a significant role in the development of hypothyroidism whereby females were less likely to develop hypothyroid, 44.4 % vs 55.6 % in males (12). In contrast, this study showed that females tend to become hypothyroid more than their male counterpart, 83.9 % vs 16.13 %. Study by El-Sayed et al. also found that female had higher predilection to develop hypothyroidism although the difference was not significant with a p value of only 0.416 (24). A possible explanation for the discrepancy between the findings of this study and the earlier study by Mohamed was that male is usually more resistant to RAI hence requiring more time to achieve successful outcome of either euthyroid or hypothyroid (12). This was however not observed in this study as female has higher rate of treatment failure when compared to male (83.3 % vs 79.6 %). Nonetheless, this finding was not statistically significant (p >0.950).

There were several limitations of this study that we would like to point out. Determination and measurement of TRAb was not done for all patients as it is not readily available in most centres in this region. Hence the application of the Modified Marinelli's formula as proposed by Szumowski was made with the assumption that most patient would have a TRAb value of <10. In addition, the effective half-life of iodine in the goitre of the study subjects was also assumed to be 5.5 days as described by Szumowski but this may not be the case in all of the patients. Hence, these assumptions may influence the outcome of RAI. Another limitation that we encounter was having to exclude patients receiving RAI of >30 mCi. There were several patients with large goitres and calculated dose of >30mCi, unfortunately did not received the full dose of RAI based on calculation as in our centre, hyperthyroidism is treated as outpatient basis and the local regulation stipulated a maximum dose of <30 mCi to be prescribed for outpatient. The exclusion of this group of patients restricted us from analysing the full extent of the effect of large goitre towards the outcome of RAI as well as limit the assessment of the effectiveness of this method in treatment of large goitre. However, this study demonstrated that patients with large goitres who received RAI dose less than the calculated dose and who were excluded from this study all failed to be rendered euthyroid or hypothyroid at 6-months and required further RAI treatment. This in turn prove the benefit of performing thyroid scintigraphy with Quantitative SPECT/CT to screen patient who may or may not benefit for RAI hence ensuring this group of patients would receive appropriate definite therapy such as surgery upfront.

Conclusion

Quantitative SPECT/CT utilising 99mTc-pertechnetate for dose determination of RAI is indeed a feasible, convenient, and reliable method in the delivery of personalised treatment to patients with hyperthyroidism. The calculated RAI dose method produced an excellent outcome with 80.3% success rate at 6 months as compared to the retrospective cohort with success rate of only 60 % (p <0.05). Thyroid gland volume is a significant determining factor in influencing treatment success with larger thyroid gland increases chance of treatment failure.

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Conflicts of interest/Competing interests

The author and co-authors had no conflict of interest to disclose which may influence the impartiality of this study.

Ethics approval

Research protocol and procedures performed were in accordance with the ethical standards of the Helsinki Declaration of 1964, revised in 2013 and Malaysian Guideline for Good Clinical Practice (1, 2). This study has

been approved by the Jawatankuasa Etika Penyelidikan Manusia, JePEM (Human Research Ethics Committee) of Universiti Sains Malaysia with USM JEPeM ID: USM/JEPeM/17120686 dated 17th May 2018.

Consent to participate

Written informed consent to participate were obtained from all participants prior to initiation of the study. Confidentiality was strictly maintained, and data rendered anonymous.

Consent for publication

Written informed consent for publication of case and study data were obtained from all participants prior to initiation of the study. Confidentiality was strictly maintained, and data rendered anonymous.

Availability of data and material

Data were taken from patients' record and institution online patient information system.

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