ASSESSMENT OF RADIOIODINE CLEARANCE IN DIFFERENTIATED THYROID CANCER PATIENTS IN HOSPITAL KUALA LUMPUR

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DECLARATION

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

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ABDULLAH HANIF BIN ROSDI

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List of Abbreviations

ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ATA	American thyroid association.
BSS	International Basic Safety Standard
DTC	Differentiated thyroid carcinoma
EDR	External dose rate
FTC	Follicular thyroid cancer
GBq	Giga Becquerel
HPE	Histopathological examination
I-131	Iodine-131; radioactive iodine
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
MOH	Ministry of health.
NCRP	National Council on Radiation Protection and Measurement.
NRC	Nuclear Regulatory Commission
mCi	miliCurie
μSv	microsievert
mSv	milisievert
mSv/H	milisievert per hour
mIU/L	mili-International Unit per litre

MBq	Mega Becquerel
MREC	Medical Research Ethics Committee
PTC	Papillary thyroid cancer
RAI	Radioactive iodine ablation
RBA	Retain body activity
Serum TSH	Serum thyroid stimulating hormone.
Serum TG	Serum thyroglobulin
USG	Ultrasound
WBS	Whole body scan

Abstrak

Penilaian penguraian radioaktif iodin di kalangan pesakit *"differentiated thyroid carcinoma"* di Hospital Kuala Lumpur.

Pendahuluan: Rawatan radioaktif iodin telah lama digunakan sejak tahun 1950-an lagi untuk merawat pelbagai jenis penyakit barah dan penyakit bukan barah. Ia adalah jenis rawatan yang paling popular, digunakan secara meluas, efektif dan selamat bagi kategori bahan radio aktif terapi yang tidak bertutup. Walau bagaimanapun, disebabkan oleh sinaran "gamma" yang dipancarkan olehnya yang boleh merangsang kesan sampingan "stochastic" terhadap orang awam regulasi radiasi untuk I-131 telah diperkenalkan. Setiap negara ada regulasi masing-masing bagi menentukan tempoh isolasi yang sesuai sebelum pesakit dibenarkan pulang. Akta Perlesenan Tenaga Atom 1984 (Akta 304) telah menetapkan pesakit hanya dibenarkan pulang apabila pancaran kadar radiasi di bawah aras 50μSv/H, atau bersamaan 1100MBq jumlah aktiviti radiasi di dalam badan.

Tujuan: Untuk mengkaji tempoh pengasingan yang sesuai bagi pesakit kanser tiroid yang menerima rawatan radio aktif iodin di Hospital Kuala Lumpur.

Metodologi: Pesakit barah tiroid jenis "differentiated" yang dirujuk bagi tujuan rawatan radioaktif iodin telah diambil sebagai pesakit untuk penyelidikan. Jumlah

semua pesakit adalah 170 orang dan mereka dibahagikan kepada 4 kumpulan mengikut jumlah iodin yang diterima (80mCi, 100mCi, 120mCi and 150mCi). Kadar pancaran radiasi diukur pada 6, 18, 24, 48 and 72 jam selepas pesakit menerima rawatan menggunakan “ionising chamber survey meter”. Graf kadar radiasi dengan masa dicipta dan segala maklumat klinikal dianilisis menggunakan perisian IBM SPSS.

Keputusan: Purata separuh masa penguraian iodin ialah 14.57±1.03 jam iaitu bersamaan dengan 14 jam 34 minit. Faktor jantina dan dos iodin yang diberikan mempengaruhi kadar penguraian iodin, masing-masing menunjukkan nilai $p=0.006$ dan $p<0.001$. Manakala, tiada perbezaan ketara kadar penguraian iodin jika dibandingkan dengan faktor jenis kanser tiroid, bangsa dan umur. Sebanyak 167 orang daripada 170 orang (98.2%) mempunyai kadar radiasi di bawah paras 50μSv pada 48 jam.

Kesimpulan: Tempoh pengasingan yang ideal bagi rawatan iodin untuk pesakit tiroid di Hospital Kuala Lumpur yang mempunyai fungsi buah pinggang yang normal tanpa mengira bangsa, dos iodin yang diterima, jantina dan umur ialah 48jam.

Abstract

Assessment of radioiodine clearance in differentiated thyroid cancer patients in Hospital Kuala Lumpur.

Introduction: Radioiodine treatment has long been used since 1950's for the treatment of various malignancy and non-malignancy diseases. It was the most popular, widely used, effective and safe unsealed source of radionuclide therapy. However, due to high gamma energy emitted from it which may induce stochastic effect to the public, radiation regulation has been introduced. Different countries have their own regulation regarding period of hospitalization needed before patient can be released to the public. Atomic Energy Licensing Act 1984 (Act 304) has stated that patient shall be discharged from isolation once the external dose rate falls below 50μSv/H which is equal to retained body activity of 1100MBq.

Aim: To assess the appropriate isolation period of radioactive iodinated thyroid cancer patients in Hospital Kuala Lumpur.

Material and methods: Differentiated thyroid cancer patients referred for radioactive iodine treatment were recruited in this study. Total participants were 170 and divided into 4 groups based on I-131 doses given (80mCi, 100mCi, 120mCi and 150mCi). External dose rate was measured at 6, 18, 24, 48 and 72 hours after ingestion of I-131 using ionising chamber survey meter. Graph of

radioactivity versus time was plotted and clinical data was analysed using IBM SPSS software.

Results: Mean effective half-life of I-131 is 14.57±1.03 hours which is equal to 14 hours and 34 minutes. Initial dose of I-131 and gender had significantly influenced iodine clearance with p value of 0.006 and <0.001 respectively. Conversely, the types of thyroid cancer, races and age do not have significant impact on iodine clearance. One hundred and sixty seven out of 170 patients (98.2%) had radiation level below 50μSv at 48 hours.

Conclusion: Ideal isolation period for I-131 treatment for thyroid cancer patient with normal renal function in Hospital Kuala Lumpur regardless of ethnics, iodine doses, gender and ages is 48 hours.

Keyword: Differentiated thyroid carcinoma, iodine-131, effective half-life, patient discharge, external dose rate, radiation safety.

CHAPTER ONE

RESEARCH BACKGROUND

1.1 Introduction

Approximately 5% of women and 1% of men worldwide have thyroid nodule diseases. These nodules have possibility to progress into malignancy in about 5-15%. Risk of thyroid cancer increased with history of head, neck and total body irradiation; strong family history of thyroid cancer, hoarseness of voice, rapid growth of the nodule and FDG avidity of thyroid nodule (American Thyroid Association Guidelines Taskforce on Thyroid *et al.*, 2009; Haugen *et al.*, 2016).

Thyroid cancer attributes to 1% of total malignancy and the most common endocrine malignancy. The incidence of thyroid cancer all over the globe has been increasing over the last decade due to improvement of imaging modalities to detect even thyroid microcarcinoma (<1cm) and rising in public awareness towards thyroid cancer itself. Majority of thyroid cancer cases were differentiated thyroid cancer (DTC) (90%) followed by medullary thyroid cancer (5-8%), poorly differentiated thyroid cancer (1-6%) and anaplastic thyroid cancer. Among all of them, DTC has a good response towards treatment and better prognosis and survival rate (F. Pacini, 2012).

DTC is further divided into papillary (85%), follicular (10%), Hurtle and oxyphil subtypes (3%). Papillary subtype tends to spread through lymphatic chain while follicular disseminated through blood supply. Hurtle subtype is variant of papillary thyroid carcinoma but behaves like follicular variant (*Nuclear Oncology: Pathophysiology and Clinical Applications*, 2012; *The Pathophysiologic Basis of Nuclear Medicine*, 2006; Ziessman *et al.*, 2013). All these variants expressed TSH

receptor on the cell membrane (sodium iodide symporter) which responds towards TSH stimulation by increasing thyroid specific protein secretion (thyroglobulin) and also speed up the rate of cancer cells growth (American Thyroid Association Guidelines Taskforce on Thyroid *et al.*, 2009; Haugen *et al.*, 2016).

Patients who are having DTC are stratified into 3 groups (high, intermediate and low risk) based on HPE, completion of surgery, serum TG, metastasis and Iodine WBS findings (table 1.1). All thyroid cancer guidelines agreed that high risk patient should undergo total or near total thyroidectomy followed by radioactive iodine (RAI) and TSH suppression therapy. These will improve in disease prognosis, reducing rate of recurrences and improve overall survival. On the other hand, remnant ablation may be indicated to intermediate risk patient whereas it is not necessary (weak recommendation) in low risk patient. Nearly 70% of loco-regional lymphadenopathies and pulmonary micro metastasis successfully cured with RAI treatment (F. Pacini, 2012; Haugen *et al.*, 2016; Perros *et al.*, 2014; Watkinson and British Thyroid, 2004).

Table 1.1 ATA 2009 Risk Stratification System with Proposed Modifications (Source: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer).

Low risk	Papillary thyroid cancer (with all of the following): a) No local or distant metastases; b) All macroscopic tumour has been resected c) No tumour invasion of loco-regional tissues or structures d) The tumour does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) e) If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan. f) No vascular invasion Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion. Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated.

Intermediate risk	Microscopic invasion of tumour into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first post-treatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension Multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutated.
High risk	Macroscopic invasion of tumour into the perithyroidal soft tissues (gross ETE). Incomplete tumour resection. Distant metastases. Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node >3 cm in largest dimension. Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion) .

Aims of RAI therapy (Haugen *et al.*, 2016; Perros *et al.*, 2014; Zhang *et al.*, 2014):

I. To improve and prolong patient survival.
II. To reduce risk of local and distant tumour recurrence by eradicating residual microscopic tumour foci and thyroid tissue post operatively.
III. To provide reassurance to patients that they are free of disease with undetectable serum thyroglobulin (TG), negative clinical examination and negative finding of imaging modalities (USG and thyroid WBS).
IV. Increased sensitivity of TG monitoring facilitating early detection of recurrence or metastatic disease.

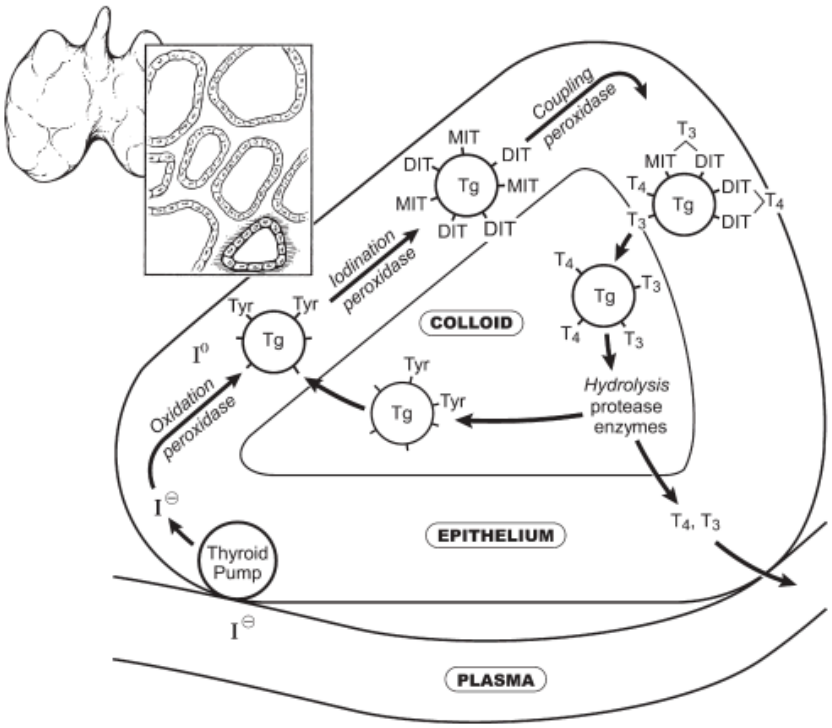
I-131 is produced in nuclear reactor by fission of uranium atom. It decays into Xe-131 by emission of Beta (606 KeV) and Gamma (364 KeV) energies. The physical half-life of the radionuclide is 8 days. The β-energy emitted with mean range in soft tissue of 0.4 mm is responsible for the therapeutic effect by inducing 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. Meanwhile γ-energy is used for imaging purposes and calculation of the radioiodine thyroid uptake ratio (Bonnema and Hegedus, 2012).

Even though International Atomic Energy Agency (IAEA) and International Commission on Radiological Protection (ICRP) has stated that there is no dose limit to patients, the maximum permissible doses can be prescribed are limited to the absorbed dose of I-131 to bone marrow and radioactivity retention in the lung. In general, the range of radioactive iodine treatment activity is between 1.1GBq up to 11.1GBq (30-300mCi) (Ravichandran, 2014; *Release of Patients After Radionuclide Therapy*, 2009; Willegaignon *et al.*, 2006). Absolute contraindications for I-131

therapy are pregnancy and breastfeeding while relative contraindication includes urinary incontinence and patient who is unable to follow regulation safety post iodine treatment.

After ingestion of I-131, up to 90% of iodine will be reduced to iodide in proximal small bowel within one hour. These iodides are trapped by follicular cell by high energy sodium iodide symporter and will be concentrated 25-500 times greater than plasma level. After that, it will be oxidized to iodine by thyroxine peroxidase, which binds to tyrosine residues on thyroglobulin. These monoiodinate and diodinate are coupled to form triiodothyronine (T3) and thyroxine (T4) and stored in colloid. Radioiodine is metabolised in the liver and muscle (*The Pathophysiologic Basis of Nuclear Medicine*, 2006; *Release of Patients After Radionuclide Therapy*, 2009; Ziessman *et al.*, 2013).

Figure 1.1 Metabolism of I-131 (Source: *Nuclear Medicine,The Requisites 4th edition).*



Many factors may influence retention of I-131 in the body such as renal function, TSH stimulation, amount of thyroid tissue, metastatic foci, diet, age, body mass, gender and race. I-131 is rapidly excreted from the body in the first 48 hours by urine which attributed to more than 80% of I-131 clearance, whereas up to 6% through feces and insignificant clearance through sweat, saliva and exhalation. (American Thyroid Association Taskforce On Radioiodine *et al.*, 2011; HAYS, 1993; Matovic, 2013; Matovic *et al.*, 2009; Pacilio *et al.*, 2005; *Release of Patients After Radionuclide Therapy*, 2009; Remy *et al.*, 2008; Willegaignon *et al.*, 2006).

Disadvantages of RAI therapy includes anxiety, inconvenience and other psychological burden due to isolation, lack of isolation room to cater increasing number of DTC cases every year, restricted daily activity with family, friends and

public for 8 days. Female patients who received RAI therapy shall delay the pregnancy for at least 6 months and stop breastfeeding 2 months before and discontinue for good after the treatment. This precaution is to prevent I-131 in the milk from reaching the infant, as well as to limit the radiation of breast tissue (Lee and Park, 2010; *Release of Patients After Radionuclide Therapy*, 2009).

Complications of I-131 can be divided into two – early and late. Early complications include sialadenitis, exacerbation of exophthalmos, xerostomia, tumour swelling, radiation thyroiditis, gastritis, nausea and vomiting. Late complications are transient infertility in male, chronic sialadenitis and xerostomia, radiation cystitis, agranulocytosis, secondary malignancy and pulmonary fibrosis (*The Pathophysiologic Basis of Nuclear Medicine*, 2006; Ziessman *et al.*, 2013)

1.2 Malaysian scenario

There were 21,773 cancer cases were reported among Malaysians in Peninsular Malaysia in the year 2006 with incidence rate of 131.3 per 100000 of population. Among all cancers, thyroid carcinoma was placed in 6th position of most common cancer after breast, colorectal, lung, cervix and ovary carcinoma, which comprises 4.1% of all cancer cases registered in Malaysia. (*MALAYSIAN CANCER STATISTICS 2006 - DATA AND FIGURE PENINSULAR MALAYSIA*, 2006). According to the latest 2007-2011 Malaysia Cancer Registry Report, DTC were ranked ninth and seventeenth for female and male respectively among all malignancy in Malaysia (Azizah Ab M, 2016).

Based on retrospective study in Hospital Kuala Lumpur from 1995 to 2000, total numbers of thyroid cancer were 107 cases (Abdullah, 2002). Differentiated

thyroid cancer accounted for 91.5% of all thyroid cancer (98 cases) with papillary thyroid cancer as the main histological variant (74 cases).

Almost similar study was done by pathology department of Hospital Universiti Sains Malaysia (HUSM) from 1994 to 2004 involving 1486 specimens (Nor Hayati Othman, 2009). It was reported that thyroid cancer incidence of all thyroid nodule cases was as high as 28.1%. Papillary thyroid cancer was the most common thyroid malignancy (76.6%). Median age of thyroid nodule was 40.0 years with female to male ratio 6:1.

Currently, there are 24 nuclear medicine centres (Ministry of Health, university and private hospital) in Malaysia but only 9 centres are providing radioactive ablation for thyroid cancer. The commonly given activity to the patient ranging from 1.1GBq to 7.4GBq (30-200mCi) based on risk stratification of the patient. Instead of giving empirical (fixed) I-131 dose, personalised dose approach based on I-131 dosimetry has become more popular in other countries. However, there is only one centre in Malaysia (National Cancer Institute in Putrajaya) using dosimetry as reference to appropriate doses to the patient.

Atomic Energy Licensing Act 1984 (Act 304) has stated that patient shall be discharged from isolation once the external dose rate falls below 50μSv/H (*Atomic Energy Licensing Act 1984*). There is variance in period of isolation for I-131 ablation patients among nuclear medicine centres based on theirs' standard of procedure. The current isolation period in Hospital Kuala Lumpur for TSH withdrawal patient is 4-5 days whereas for patient with recombinant TSH (Thyrogen) is 3 days.

CHAPTER TWO

LITERATURE REVIEW

Radiation hazard emitted from unsealed source of radionuclide that has been administered patients has been a cause of concern to the public. Alpha and beta emitters have short travel distance and deposit all their energies within patient's body. The only way radiation hazard can occur is by poor handling of patient's body fluid and excreta, which attribute to <10% of radiation hazard to the public. Meanwhile, gamma and x-rays have low energy transfer to the soft tissue and being emitted outside patient's body. The amount of radiation received by public is depends on the types and amount of energy emitted, half-life and biokinetic of radionuclides; retained radioactivity in the body; distance and duration of exposure (American Thyroid Association Taskforce On Radioiodine *et al.*, 2011; Poon *et al.*, 2016; *Release of Patients After Radionuclide Therapy*, 2009).

As mentioned before, I-131 does not only emitting beta particle, it is also emitting high energy gamma (364KeV). Historically, the patient isolation is based on physical half-life of the radionuclide substances. This method has been proven to be inaccurate and causing unnecessary difficulties to the patient and high cost to the health service. The best way to estimate isolation period is by using effective half-life. Physical half-life is the time needed for the radionuclide to achieve half of the initial activity during its decay to stable nuclide. Biological half-life is the time needed for the radioactive substance to reach half of its initial value by biological elimination. Effective half-life is the time needed for the radionuclide deposited in the living organism to reach half of its initial value by the combined action of physical and biological decay.

There are 3 methods used to estimate effective half-life of radionuclide (Remy *et al.*, 2008; Thomas *et al.*, 1980):

1. Measurement of urine iodine (urine assay) as retained body activity (RBA).
2. External dose rate (EDR) using ionising chamber survey meter.
3. Dosimetry calculation based on I-131/I-123 diagnostic WBS prior ablation.

Only the first two were implemented as rules and regulations to determine period of isolation. In Turkey, 83 patients were recruited to establish connection between RBA and EDR and to determine duration of isolation (Demir *et al.*, 2013). The monitoring of RBA and EDR were lasted for 5 days. The estimated effective half-life was 18.4 hours for EDR and 18.7 hours for RBA. Similar study was done in China involving 70 patients (Zhang *et al.*, 2014). Both studies conclude that there was strong positive correlation between EDR and RBA and no significant difference in period of isolation by using either methods. EDR is proven to be safe, simple and reliable method.

Calculation formula to determine I-131 effective half-life (Krane, 2008):

$$A = A_0.e^{-\lambda t}$$

A = current radioactivity

A_0 = initial radioactivity

λ = decay constant

t = half life

The half-life, $t_{1/2}$, is defined as follows:

$$\frac{A\ (t + t\frac{1}{2})}{A\ (t)} = \frac{1}{2} = \frac{\mathrm{A0exp}\ (-\lambda t - \lambda t\frac{1}{2})}{\mathrm{A0exp}\ (-\lambda t)} = \exp(-\lambda t\frac{1}{2})$$

$t_{1/2}$ (**effective half life**) $= \frac{\log 2}{\lambda}$

Calculation formula to determine biological half-life:

$$\frac{1}{\text{effective half life}} = \frac{1}{\text{biological half life}} + \frac{1}{\text{physical half life}}$$

Biological half life $= \frac{(\text{physical half life})\ (\text{effective half life})}{\text{physical half life} - \text{effective half life}}$

International Basic Safety Standard (BSS), European Commission, National Council on Radiation Protection and Measurement (NCRP), International Atomic Energy Agency (IAEA) and International Commission on Radiological Protection (ICRP) have set up radiation dose limit to the public into two groups; family members/close friends and third person (Table 2.1) (Beckers, 1997; Commission, 1998; *Release of Patients After Radionuclide Therapy*, 2009)

Table 2.1 Dose limit to the public based on IAEA and ICRP recommendation (Source: Release of patients after radionuclide therapy; Safety Report Series No. 63)

Type of person	Dose constraint (mSV)
1. Third person	0.3/episode
2. Family members/close friends	
• Pregnant women	1/year
• Children up to 2 years	1/year
• Children 3-10 years old	1/episode
• Children 11 years old up to 60 years old	3/episode
• Adult older than 60 years old.	15/episode
• Comforter/Carer	5/episode

:

Comforter/carer is an adult who assists, supports and provides comfort to patient and willingly accepts exposure to radiation after appropriate explanation by medical staff. It can be a single person, two or more.

Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) have put out regulations that state the restricted dose to the public is 1mSv/year and <5mSv/treatment episode for carer/comforter (*Recommendations for the Discharge of Patients Undergoing Treatment with Radioactive Substances*, 2002; Vetter, 1997). Radiation restriction in the United State of America is less stringent and simple compared to the others. According to the United State Nuclear Regulatory Commission (NRC), the effective dose to public either family member, comforter or third person must be less than 5mSv/year (American Thyroid Association Taskforce On Radioiodine *et al.*, 2011; North *et al.*, 2001; *Release of Patients After Radionuclide Therapy*, 2009)

Based on the recommendations above, countries over the globe developed their own nuclear regulation by considering many aspects and factors such as health status, socioeconomic background, domestic activity, home circumstances, waste disposal and health facilities. As a result, the radiation limit and isolation period are varied and not harmonised (Table 2.2) (Beckers, 1997; Demir *et al.*, 2013; Lee and Park, 2010; Nantajit *et al.*, 2015; Pacilio *et al.*, 2005; Ravichandran *et al.*, 2010; Ravichandran, 2014; *Recommendations for the Discharge of Patients Undergoing Treatment with Radioactive Substances*, 2002; *Release of Patients After Radionuclide Therapy*, 2009; Tabei *et al.*, 2012; Venencia *et al.*, 2002; Vetter, 1997; Zhang *et al.*, 2014).

Table 2.2 Regulation to discharge radio iodinated patient across the globe.

Country	Retain Body Activity (MBq)	External Dose Rate (μSv/h)
USA Korea	<1200	<70
EU states Germany Switzerland & Austria Turkey Poland, Greece, Hungary, Italy & Sweden UK, France & Belgium	75 to 800, most member state 400-600 <75 <170 <400 <600 <800	 <3.5 <10 <20 <25 <40
Malaysia, Thailand & Argentina	<1100	<50
Australia	<600	<25
Japan	<500	
China	<400	<20
Oman & Iran	<170	<10
IAEA recommendation	<1100	<50
ETA recommendation	<800	<40

According to the local rules, all patients who received I-131 treatment either for thyrotoxicosis or thyroid cancer in Germany must be hospitalised at least for 2 days (*Release of Patients After Radionuclide Therapy*, 2009). Thyroid cancer patients in France, Argentina, Thailand and Korea are commonly isolated for 2 night and 3 days while in Italy the isolation period maybe up to 4 days.

CHAPTER THREE

OBJECTIVES AND HYPOTHESES

3.1 General objective

- To establish the ideal isolation period for DTC patients who receive I-131 ablation therapy in Hospital Kuala Lumpur.

3.2 Specific objective

1. To study the external dose rate (EDR) as function of time.
2. To estimate effective and biological half-life of radioactive iodine.
3. To determine isolation period based on I-131 doses.
4. To evaluate other factors that may contribute to iodine clearance (patient related and disease related).

3.3 Hypothesis Statements

- Alternate hypothesis: Ideal isolation period for I-131 ablation patient is within 48 hours.
- Null hypothesis: Ideal isolation period for I-131 ablation patient is longer than 48 hours.

3.4 Rationale of the study

a) Different culture, climate, dietary and race contribute to the differences in iodine metabolism.
b) The current isolation period of 4-5 days does not reflect Malaysia's patient release regulation (<50μSv), which is higher compared to other countries.
c) To establish local data regarding period of hospitalisation which shall be applied in future practice.

3.5 Benefit of the study

If the research hypothesis proves to be true, the followings benefit or impact shall be observed:

1. Increase bed turnover in centre with limited number of bed for isolation, hence, it will reduce patient waiting list for I-131 ablation.
2. It provides patient comfort and convenience by shortening the duration of hospitalisation without violating the radiation regulation and causing additional harm to the public.

CHAPTER FOUR

Methodology

4.1 Study Design, Study location and Study Period

A prospective observational study was carried out in the Department of Nuclear Medicine of Hospital Kuala Lumpur from the period of March 2016 till December 2017.

4.2 Study population and sample

The reference population in this study was differentiated thyroid carcinoma patients who underwent total or completion thyroidectomy in Malaysia. Those who were referred to the Nuclear Medicine Department, Hospital Kuala Lumpur for I-131 ablative therapy was the source population. The study participants were those who consented to participate in this study and fulfilled the inclusion and exclusion criteria.

4.3 Inclusion criteria:

1. Differentiated thyroid cancer patients post total or near total thyroidectomy (papillary, follicular and Hurtle cell carcinoma).
2. Patients adhered to the I-131 ablation preparation as mentioned below:
    i) Stop thyroxine for a month and stop high iodinated food for 2 weeks.
    ii) No recent iodine contrasted agent (six weeks and below).
    iii) Stop iodine containing medication such as amiodarone 3 months prior to ablation.
3. Patients with adequate TSH stimulation (Serum TSH level >30mU/L).
4. Patients with good renal function – serum creatinine <110μmol/L.

4.4 Exclusion criteria:

1. Pregnant patient.
2. Patient who received recombinant human thyroid stimulating hormone (Thyrogen).

4.5 Sample size calculation

Single Proportion calculation was used to derive the sample size of 164 I-131 ablation therapy patients. This number provided 95% confidence level, 80% study power and 3% precision, as the prevalence of thyroid cancer patients is 4% of all malignancies in Malaysia (*MALAYSIAN CANCER STATISTICS 2006 - DATA AND FIGURE PENINSULAR MALAYSIA*, 2006) Appendix A.

4.6 Statistical analysis

The patient's descriptive data were described by mean (standard deviation) or median (interquartile range), depending on normally distributed or skewed data. The categorical variable was reported as frequency and its percentage. ANOVA test was used to test the significant difference in estimated effective half-life clearance of radioactive I-131 within time. The difference of I-131 effective half-life between age group and gender was assessed using independent sample t-test/ Mann-Whitney U test.

The difference between I-131 doses was measured using one-way ANOVA/ Kruskal-Wallis test. Fisher's exact test was used to determine the association of the variables (age group, gender, dosage, race, etc.) with number of days in the ward (≤48 hours and >48 hours).

For all analyses, *p* values less than 0.05 were considered statistically significant. Analyses were performed using SPSS version 24.0 (SPSS Inc. Chicago, Illinois, USA).

4.7 Variable definition

a) Differentiated thyroid cancer - 3 histology types: papillary, follicular and Hurtle cell.

b) Age: <45 and ≥45 years based on TNM thyroid cancer staging system.
    - Based on TNM staging, patients are categorised into two groups (<45 and ≥45 years old. In the first group, there is only 2 stages of thyroid cancer (stage I and II) while in the second group, there is 4 stages (table 4.1) (Yannello, 2013). Patients in the first group have better prognosis compared to the second group.

c) Gender: female and male.

d) I31 ablation doses: 80mCi, 100mCi, 120mCi and 150mCi.
    - The I-131 doses given in Nuclear Medicine Department of Hospital Kuala Lumpur were based on ATA risk stratification (Table 1.1). 80mCi was given to the low risk group, 100mCi to the intermediate risk group without evidence of lymph node metastasis, 120mCi to the intermediate risk group with evidence of lymph node metastasis and 150mCi for the high risk group.

Table 4.1 Differentiated Thyroid Cancer Staging (Source: 7th edition of the AJCC Cancer Staging Manual).

Differentiated thyroid cancer under 45 years

Stage I	Any size tumour, located in the thyroid or spread to local lymph nodes and tissue.
Stage II	Any size tumour which has spread to other organs.

Differentiated thyroid cancer 45 years or over

Stage I	Located only in the thyroid; 2 cm or smaller.
Stage II	Located only in the thyroid; 2-4cm.
Stage III	➢ Tumour is larger than 4cm and only in the thyroid bed. ➢ Any size tumour which has spread outside the thyroid and to the central compartment lymph nodes of the neck
Stage IVA	➢ Any size tumour which has spread to the trachea, oesophagus, larynx or laryngeal nerve. ➢ Any size tumour which has spread to the lateral compartment lymph nodes of the neck.
Stage IVB	Any size tumour which has spread to the spinal column or surrounds major blood vessel.
Stage IVC	Any size tumour which has spread to other organs.

4.8 Research protocol

1. The medical officer of Nuclear Medicine Department screened new cases from surgical/ENT departments.
2. All the new cases were discussed with nuclear medicine physicians to decide the appropriate dose to patients according to ATA risk stratification every Thursday (Table 1.1).
3. The dose for follow up cases has already been decided during the previous clinical visit based on the serum Thyroglobulin level, ultrasound findings and whole-body scan imaging.
4. The patients were contacted and instructed to stop thyroxine for a month and food with high iodine content such as seafood, turnip and cabbage for 2 weeks.
5. The patients were recruited on the day of admission by the primary investigator.
6. The patients received written information (consent form) concerning I-131 treatment and radioprotection (Appendix B & C).
7. The renal profile, TFT, serum TG and anti-TG antibody were taken at the clinic.
8. The I-131 strength was assayed in dose calibrator 'Atomlab^{TM} 400' (figure 4.1).
9. I-131 was administered to the patients according to their individual doses.
10. The patients were instructed to hydrate themselves with copious fluid intake in isolation ward.

11. EDR were measured using hand held type ionising chamber survey meter 'Victorin 451 P' (figure 4.2) by measuring range 0.1μSv/h to 100μSv/h (calibrated annually using Caesium 137).
12. The radiation exposure was measured by asking the patients to stand 1 meter away from the survey meter.
13. EDR measurements were taken at 6H, 18H, 24H and daily for the next 3 days. (Current practice only measuring EDR on the day of discharge to make sure radiation emitted by patient is below 50μSv).
14. Patients' data were collected and analysed using SPSS version 24.0.

Figure 4.1: Dose calibrator Atomlab™ 400.