RADIOIODINE-131 THERAPY IN LOW RISK WELL DIFFERENTIATED THYROID CARCINOMA: COMPARISON BETWEEN FIXED DOSES VERSUS VARIABLE DOSES BASED ON TECHNETIUM-99m PERTECHNETATE UPTAKE RATE

By:

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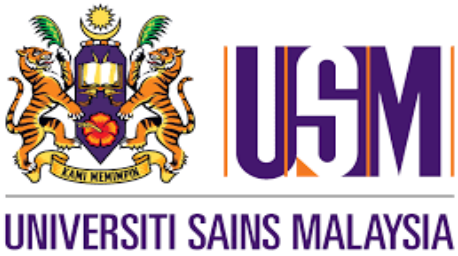
Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Master Of Medicine (Nuclear Medicine)



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ABBREVIATION AND UNITS

Tg	Thyroglobulin
TFT	Thyroid function test
TSH	Thyroid stimulating hormone
Tc-99m	Technetium-99m
T3	Triiodothyroxine
T4	Thyroxine
TRH	Thyroid releasing hormone
TNM	Tumor, lymph node and distant metastasis
N	Lymph node
ATA	American thyroid Association
AJCC	American Joint Committee against Cancer
UICC	Union International Contre le Cancer
I-131	Radioiodine-131
WBS	Whole body scan

Unit	
KeV	Kilo electronvolt
MeV	Mega electrovolt
MBq	Mega Bacquerel
mCi	mili Curie
mGy	mili Gray
ug/L	microgram per Litre
mIU/L	mili-International Unit per Litre
pmol/L	picomoles per Litre
≤	equal and less than
>	more than

ABSTRAK

Pengenalan: Pembedahan tiroid diikuti oleh rawatan radioaktif iodin-131 untuk memusnahkan mana-mana sel tiroid yang tertinggal merupakan satu kaedah untuk merawat pesakit yang menghidapi penyakit kanser tiroid. Berdasarkan garis panduan ATA (2009), amalan semasa adalah dengan memberi dos di antara 30 sehingga 100 mCi kepada pesakit kanser tiroid yang berisiko rendah.

Objektif: Tujuan kajian ini adalah untuk membuat perbandingan kadar kejayaan dos tetap radioaktif iodin-131 dengan dos radioaktif iodin-131 yang pelbagai berdasarkan kadar pengambilan Tc-99m pertechnetate oleh tiroid untuk rawatan pesakit kanser tiroid yang berisiko rendah.

Kaedah: Seramai 53 pesakit (47 perempuan dan 6 lelaki dengan purata umur 41.3 $\pm$ 13 tahun) yang telah disahkan menghidap kanser tiroid yang berstatus risiko rendah (N0 dan M0) dan telah menjalani pembedahan tiroid total dikaji secara prospektif. Mereka telah dibahagikan secara rawak kepada dua kumpulan rawatan yang berbeza. Kumpulan rawatan yang pertama, mereka diberi dos radioaktif iodin-131 mengikut dos yang telah ditetapkan sebanyak 80 mCi (n = 27) manakala satu kumpulan rawatan kedua akan menerima dos radioaktif iodin yang pelbagai (30 mCi, 80 mCi atau 100 mCi) berdasarkan kadar pengambilan Tc-99m pertechnetate oleh tiroid (n = 26). Selepas menerima rawatan radioaktif iodin-131, imbasan iodin seluruh badan dan pengambilan darah serum tiroglobulin pada 12 bulan dilakuan untuk menilai hasil kejayaan rawatan tersebut.

Keputusan: Secara kesuruhannya, seramai 19 (36%) daripada jumlah 53 pesakit yang menerima radioaktif iodin telah menunjukan kejayaan rawatan. Seramai 11 daripada 27 pesakit (41%) di dalam kumpulan rawatan radioaktif iodin-131 dos tetap telah menunjukan hasil kejayaan rawatan berbanding pesakit yang berada di kumpulan dos yang berdasarkan pengambilan Tc-99m pertechnetate yang hanya menunjukan kejayaan rawatan seramai 8 daripada 26 pesakit (31%) yang terlibat. Walau bagaimanapun, perbezaan ini adalah tidak signifikan secara statistik (p = 0.573). Mempunyai tahap serum tiroglobulin kurang daripada 2 ug/L sebelum rawatan dan tempoh rawatan kurang 4 bulan

selepas pembedahan tiroid mempunyai peluang yang lebih tinggi untuk berjaya dalam rawatan. Faktor-faktor lain seperti umur, bangsa, jantina, jenis histologi kanser tidak mempengaruhi kejayaan rawatan.

Kesimpulan: Tiada perbezaan yang signifikan di antara kumpulan rawatan radioaktif iodin-131 berdos tetap dengan kumpulan rawatan radioaktif iodin-131 pelbagai dos yang berdasarkan kadar pengambilan oleh Tc-99m pertechnetate oleh tiroid. Tetapi kadar pengambilan oleh Tc-99m pertechnetate mungkin boleh digunakan terutama sekali jika kadar pengambilannya melebihi 1.4% yang mana dos radioaktif iodin-131 yang lebih tinggi mungkin diperlukan. Kajian lanjut dengan saiz sampel yang lebih besar dan meliputi faktor-faktor lain yang lagi menyeluruh adalah disyorkan.

ABSTRACT

Title: Radioiodine I-131 Therapy In Low Risk Well Differentiated Thyroid Carcinoma: Comparison Between Fixed Doses Versus Variable Doses Based on Tc-99m Pertechnetate Uptake Rate

Introduction: Total thyroidectomy, followed by radioiodine-131 to destroy any remaining thyroid cell or thyroid cancer cell, is an established method of treatment for thyroid carcinoma. Based on ATA 2009 guideline, dose activity of radioiodine-131 between 30 to 100 mCi is recommended in low risk well differentiated thyroid carcinoma.

Objective: The aim of this study is to compare the success rate of fixed dose radioiodine-131 therapy against variable doses based on thyroid Tc-99m pertechnetate uptake rate in treatment of low risk well differentiated thyroid carcinoma.

Method: 53 patients (47 female and 6 male; mean $\pm$ SD = 41.3 $\pm$ 13 years) diagnosed with well differentiated thyroid carcinoma with N0 and M0 disease who had undergone total thyroidectomy were evaluated prospectively. They were randomly divided into two groups according to fixed doses (80 mCi) and variable doses (30 mCi, 80 mCi or 100 mCi) of radioiodine-131 based on thyroid Tc-99m pertechnetate uptake rate (n = 27 for fixed dose group, n = 26 for variable dose). All patients underwent radioiodine-131 ablation therapy followed by radioiodine-131 WBS and stimulated serum thyroglobulin monitoring to evaluate the outcome after 12 months.

Result: At 12 months, 19 (36%) patients were successfully ablated after received single dose of radioiodine-131 ablation. In the fixed dose group, 11 out of 27 (41%) patients were successfully ablated compare to variable group with 8 out of 26 patients (31%). However, the differences were statistically not significant (p = 0.573). Pre-treatment stimulated serum thyroglobulin less than 2 ug/L and duration of less than 4 months to first radioiodine-131 were associated with higher chance of successful ablation. There were no significant differences in success rates in term of age, sex, race, or histological type of primary tumour.

Conclusion: There is no significant differences in success rate between the fixed dose protocols against variable dose in remnant ablation in with low risk well differentiated thyroid carcinoma. There may be value of thyroid Tc-99m pertechnetate uptake study especially in those patients with uptake rate >1.4% who may require higher dose of radioiodine-131 to achieve success rate after one administration. Further studies with a larger sample size and covering other contributing factors are recommended.

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Endocrine malignancy is very rare, accounts for only about 1% of all human cancer. The most common endocrine malignancy is thyroid carcinoma (Elisei et al., 2013). The natural history of a disease will dictates the long term management of the patient.

Total thyroidectomy with or without neck dissection is the treatment of choice for most patients with thyroid carcinoma. All patient diagnosed with well differentiated thyroid carcinoma should undergo thyroidectomy followed by radioiodine-131 therapy to destroy the remaining thyroid tissue or thyroid cancer cell, except in patients with isolated carcinoma and the tumour size is less than 1cm (Pacini et al., 2006).

At present, there is no consensus on the best method to be used in deciding the precise dose activity of radioiodine-131 to be prescribed in the low risk well differentiated thyroid cancer patient. However, if it is administered, low activity is recommended (Haugen et al., 2016, Cooper et al., 2009). A few authors have proposed fixed dose radioiodine-131 for this group of patient (Rosario et al., 2005b, De Klerk et al., 2000) while another group's author has proposed that quantitative uptake related with varying activity (Giovanella et al., 2011, Zidan et al., 2004). The quantitative uptake techniques that are described have utilised radioiodine-124, radioiodine-131 or Tc-99m pertechnetate for deciding the activity doses of radioiodine-131 before treatment (Jentzen et al., 2008, Kueh et al., 2010, Park et al., 1994).

The use of radioiodine-124 for dosimetry is not feasible due to limited PET facilities, especially in Malaysia. Other than this, the radioiodine-131 can be used for diagnostic WBS or uptake rate study to evaluate the size of thyroid remnant before ablation. However, diagnostic radioiodine-131 WBS before ablation would cause stunning of thyroid remnant, thus reducing the success rate of radioiodine-131 ablation (Verburg et al., 2009, Bajén et al., 2000). This has resulted some author proposing the used of radiopharmaceutical Tc-99m pertechnetate as a tool for thyroid dosimetry post thyroidectomy.

The reason why Tc-99m pertechnetate is being proposed to be used for thyroid dosimetry based on these factors. Firstly, Tc-99m pertechnetate is taken up by sodium iodide symporter (NIS)

channel in follicular cell of thyroid gland similar to radioidine-131. The only different is Tc-99m pertechnetate is not incorporated into thyroid hormone or stored in the thyroid gland, due to its physiological similarity to iodine, it still widely used for investigation of thyroid nodule and functional status of thyroid gland. Second, the radiation doses to patient by Tc-99m pertechnetate is much lower compared to radioiodine-131 (Becker et al., 1996). Third, the calculation of thyroid uptake can be done much faster (within 20 min post injection) compare to radioiodine-131 uptake rate in which the uptake rate is calculated only at 24 hours. Tc-99m pertechnetate is also easily available, easy to use and does not causing stunning to remnant thyroid tissue (Kueh et al., 2010, Nadig et al., 2008). Early studies have shown the potential value of thyroid Tc-99m pertechnetate uptake rate in post thyroidectomy for pre radioidine-131 therapy. Study by Giovanella et al (2011) showed that 74 out of 77 patient (96%) with absent Tc-99m pertechnetate uptake has successful ablation after one time administration of 100 mCi radioiodine-131 after 12 month (Giovanella et al., 2011). Study by Geatti et al (2012) also has showed better post ablation outcome which follows Tc-99m pertechnetate scintigraphy in patient with negative scan (Geatti et al., 2012).

Therefore, the purpose of the present study is to assess whether Tc-99m pertechnetate uptake rate has a role to decide the doses of radioiodine-131. This is done by comparing the success rate between the empirical high fixed doses and variable doses radioiodine-131 in the treatment of low risk well differentiated thyroid carcinoma by utilising thyroid Tc-99m pertechnetate uptake rate.

1.2 BRIEF ANATOMY AND PHYSIOLOGY

The thyroid gland is an essential organ of human endocrine system. Its main function is synthesising, storing and releasing thyroid hormone into the blood circulation. It releases thyroid hormone of thyroxine (T4). Thyroxine is then converted to triiodothyronine (T3) in the periphery and regulates metabolism and organ performance (Ziessman et al., 2014).

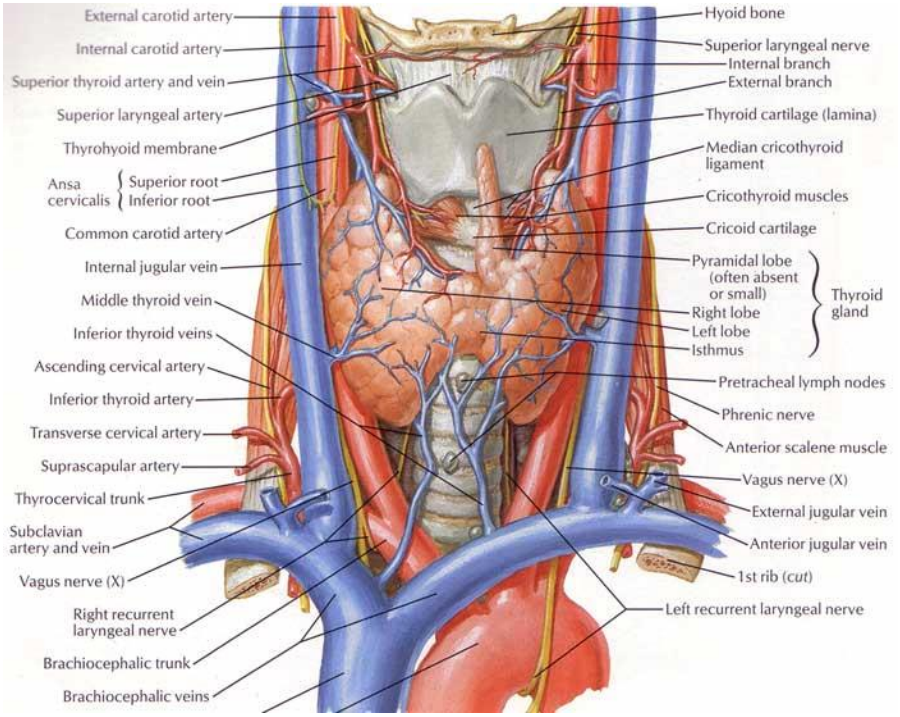

Figure 1.0 : anterior view of the thyroid gland (adapted from http://gog.net.nz/AnatomyThyroid.html access on 10.10.2016)

The thyroid gland is located just inferior to the thyroid cartilage anterior to the trachea. It has a butterfly shape consisting of two lobes (right lobe and left lobe) connected in the middle by isthmus. The thyroid gland receives blood supply from superior thyroid artery and inferior thyroid artery (Braverman and Cooper, 2012). The superior thyroid artery is a branch of external carotid artery, while the inferior thyroid artery is a branch of thyrocervical trunk. Venous drainage of the thyroid gland is to the superior, middle and inferior thyroid vein. Both parasympathetic and sympathetic nerves supply the thyroid gland (Braverman and Cooper, 2012).

The level of thyroid hormone secreted by the thyroid gland into the bloodstream is regulated by thyroid stimulating hormone (TSH). TSH is produced by a gland in the anterior pituitary. The pituitary gland controls the quantity of thyroid hormone secreted into the blood circulation. There are two glands, the anterior and posterior pituitary. Together, these glands work like a thermostat to regulate the level of thyroid hormone. These glands constantly sense the levels of T3 and T4 in the blood circulation. The hypothalamus senses low circulating level of thyroid hormone (T3 and T4) and respond by releasing thyrotropin-releasing hormone (TRH) that will stimulate the production of TSH from pituitary gland. When there is adequate level of serum TSH, it stimulates the thyroid cell to produce thyroid hormone. T4 is the main thyroid hormone released by the thyroid gland into the blood circulation and transported to the peripheral tissue by thyroid binding protein. In the peripheral tissue it is then converted to the metabolically active T3 at the site of action (Braverman and Cooper, 2012) .

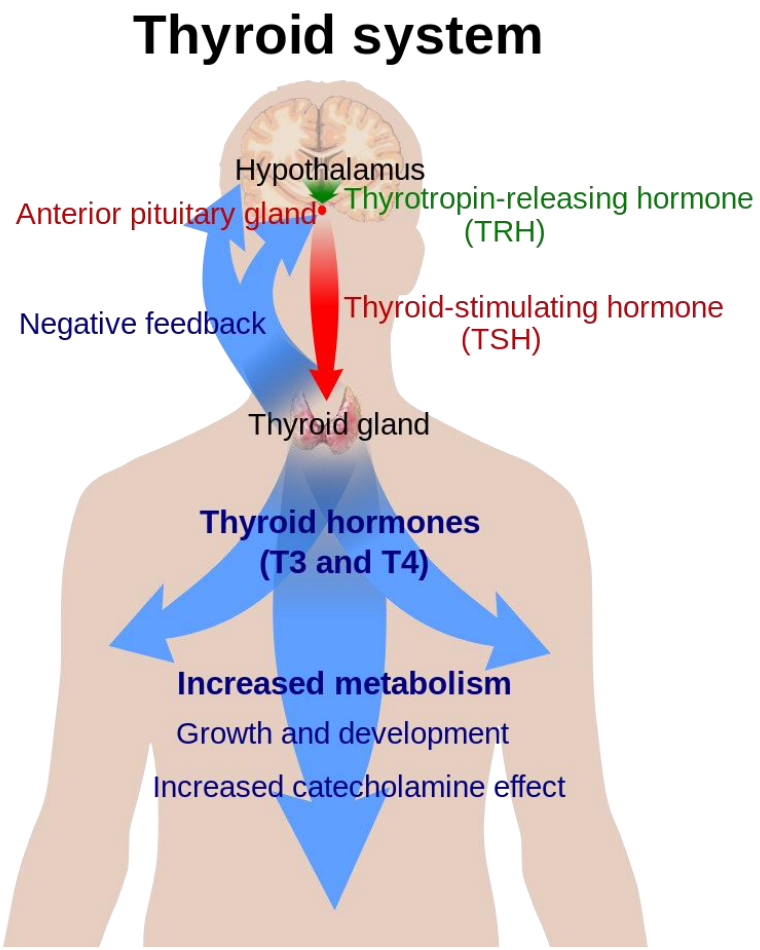

Figure 2: hypothalamus-pituitary –thyroid axis (adapted from Mikael Häggström https://commons.wikimedia.org/w/index.php?curid=8567011 access on 27.11.2016)

Iodine is extremely important component for synthesis of thyroid hormone. Iodine is reduced to iodide in the small intestine after oral ingestion. Within 60 minutes, about 90% of iodide is absorbed and distributes in the blood as extracellular ion. It exits from circulation via thyroid extraction or urinary excretion (Ziessman et al., 2014).

Thyroid follicular cell trap iodide with sodium iodide symporter followed by organification. The iodides are then oxidised to iodine by thyroid peroxidase at follicular cell colloid interface before binding to tyrosine residues on the thyroglobulin. These monoiodinated and diiodinated tyrosine are couple to form triiodothyroxine (T3) and thyroxine (T4) by thyroid peroxidase enzymes, which are then stored in the colloid of follicular lumen (Ziessman et al., 2014, Dumont et al., 1992) .

1.3 THYROID CARCINOMA

According to data and figure from Malaysia's Cancer Statistic 2007, thyroid cancer is the 9th commonest thyroid cancer in Malaysian females. It accounts for about 3.0% of all cancers among female population. The incidence rate was highest among Malays (169 cases) followed by Chinese (73 cases). It is the 9th commonest cancer in Malay and 10th for Chinese population (Omar and Tamin, 2011).

Thyroid cancer commonly arises from follicular cell or follicular C-cell but some rare thyroid cancer such as thyroid sarcoma, thyroid haemangiosarcoma and thyroid lymphoma also arises from other cells (Elisei et al., 2013). Such cancers are mainly classified according to histological features such as papillary thyroid carcinoma, follicular thyroid carcinoma, anaplastic thyroid carcinoma and medullary thyroid carcinoma (Elisei et al., 2013). The most common thyroid carcinoma is papillary thyroid carcinoma which accounts for 80% of all cases followed by follicular thyroid carcinoma which is only about 10-15% (Elisei et al., 2013). Both papillary and follicular thyroid carcinoma are defined as differentiated thyroid carcinoma (Ziessman et al., 2014). The term differentiated thyroid carcinoma is defined as cancers that arise from thyroid follicular cells. This term are is used as these types of cancers and its variants maintained the features of follicular normal cell which have the ability to take up and accumulate iodine, produced thyroglobulin and sensitive to serum thyroid stimulating hormone stimulation (Elisei et al., 2013) . Thyroid microcarcinoma is a term given to any thyroid cancer with tumour size less than 1cm in diameter (Haugen et al., 2016, Ziessman et al., 2014).

Total thyroidectomy is the treatment of choice for most patients with differentiated thyroid carcinoma. For all patients except those diagnosed with thyroid microcarcinoma, thyroidectomy should be followed by radioiodine-131 ablation to destroy the remaining tissue or thyroid cancer cell. However recent guideline by American Thyroid Association (2009) suggest the importance to risk stratified patient accordingly before decision for additional treatment such as radioiodine-131, surgery or other treatment given. Under this guideline, radioiodine-131 is not recommended to be given to patient with low risk well differentiated thyroid carcinoma. Low risk well differentiated thyroid

carcinoma is defined as a disease confined to the thyroid, lack of extensive invasion of the capsule of the tumour (follicular carcinoma), primary tumour less than 4 cm in diameter, and without nodal and distant metastases (Haugen et al., 2016). If radioiodine-131 is to be used, low activity doses are recommended (Cooper et al., 2009). However, in the nuclear medicine department, Hospital Pulau Pinang radioiodine-131 therapies are still prescribed as adjuvant therapy to those patients with low risk well differentiated thyroid carcinoma post total thyroidectomy.

1.4 CLINICAL PRESENTATION AND INVESTIGATION

Patients usually presented with a thyroid nodule, whether single or multiple nodules such as in multi-nodular goitre. These nodules have features of firm in consistency, irregular margin or fixed to tissues nearby. The presence of palpable lymph nodes in the neck, with or without rapid increase in size of nodules over weeks or months and associated with dysphagia or hoarseness, is a features pointing toward thyroid carcinoma (Elisei et al., 2013).

Although thyroid nodules are very common in patient older than 50 years old, only about 4-5% thyroid carcinoma are represented in all thyroid nodules (Elisei et al., 2013). Therefore it is vital to investigate the thyroid nodule in order to differentiate between benign and malignant lesions, as this will impact the overall management (Schlumberger et al., 2004).

Complete medical history and physical examination of neck region especially are very crucial. Patients with family history of thyroid cancer and history of radiation exposure to the neck have increased risk of malignancy (Ziessman et al., 2014). First, second, and third-degree relatives of patient with papillary thyroid carcinoma have significant risk of developing this cancer compared with population controls. First-degree relatives have 5.4 fold increased risk of being diagnosed this cancer themselves. Second and third-degree relatives have 2.2 fold and 1.8 fold increased risk respectively (Oakley et al., 2013). Direct or incidental thyroid irradiation increases the risk for developing well-differentiated papillary and follicular thyroid cancer from 15 to 53 fold (Hancock et al., 1995). Accurate palpation provides information regarding the location, sizes of nodule, consistency, motility during swallowing and present of extra nodular thyroid tissue. Examination of the neck also provides information on the extent of lymph node involvement (Elisei et al., 2013).

The recommended imaging technique to detect thyroid nodule is thyroid ultrasonography (Haugen et al., 2016, Cooper et al., 2009). It can accurately define gland volume, sizes, number and structure of the thyroid nodules, distinguishing thyroidal from extra-thyroidal mass, evaluating lymph node metastases and guiding fine needle aspiration (FNA) biopsy. Features in the ultrasound suggestive of malignancy include hypoechogenicity, irregular borders, microcalcification, absence of peripheral halo, and hypervascularity (Kuna et al., 2006).

Pre-surgical diagnosis using fine needle aspiration cytology (FNAC) is the method of choice to diagnose thyroid malignancy (Haugen et al., 2016, Cooper et al., 2009). The nature of the thyroid nodule can reliably screen and identify in remarkable degree of certainty in those patient that require surgical intervention (Hegedüs, 2004). FNAC is best performed using ultrasound guidance. This will improve diagnostic accuracy by helping to locate the exact thyroid nodule to aspirate and decrease the false negative result and inadequate sample or specimen number. The sensitivity of FNAC guided biopsy ranges from 65%-95%, specificity up to 96% and has 99% of negative predictive value (Gharib and Goellner, 1993).

1.5 THYROID SCINTIGRAPHY

Thyroid scintigraphy provides functional, non-anatomical information that assists in guiding further diagnostic procedure in patients presenting with thyroid nodule. In thyroid scintigraphy, nodules are classified as hot, cold, warm or indeterminate by comparing the nodules to salivary gland uptake. 85 to 90% of thyroid nodules are cold, as the incidence of cancer in cold nodules is about 15 to 20% (Ziessman et al., 2014).

Radioiodine-123, radioiodine-131 and Tc-99m pertechnetate are the three known radiopharmaceuticals used for thyroid scintigraphy in nuclear medicine department. Both radioiodine-131 and radioiodine-123 behave similar to iodide as they are taken up, organified, and incorporated into thyroid hormone by thyroid cell (Ziessman et al., 2014). They are the ideal physiology radiotracers which provide information of thyroid function. However, radioiodine-123 is more superior as it is a pure gamma emitter and has excellent characteristics for imaging with gamma cameras (Mandel et al., 2001).

Radioiodine-131 has a principal 364 keV of gamma photon with 8 days of physical half-life. This energy of gamma photon is not optimal for gamma camera because the count detection for radioiodine-131 is poor, with emission penetrate the collimator septa resulting image degradation. The images produced are valuable for therapy and detection of metastasis. Radioiodine-123 decayed by electron capture. It has a half-life of 13.2 hours and principal gamma emission of 159 keV. Such gamma emission is well suited for gamma camera imaging. However, it is not readily available for uses in Malaysia due to the high production costing as well as problems with availability and delivery from overseas (Ng and Mohd, 2005).

Radiopharmaceutical Tc-99m pertechnetate has been used for thyroid scintigraphy because it is readily available and has low radiation exposure dose to patient (Ziessman et al., 2014). The Tc-99m pertechnetate gamma photon energy has a photopeak of 140 keV, which make it ideal for use with a gamma camera as it as better resolution image compared to radioiodine-131 (Ziessman et al., 2014). The half-life is about 6 hours and has no particulate emission. Tc-99m pertechnetate is administered intravenously. It is taken up by the thyroid cell by similar mechanism as radioiodine or iodide but not organified or incorporated into the thyroid hormone. The thyroid will not retain it; thus,

the imaging has to be performed early at 20 to 30 minutes after injection. The doses usually used is around 1-5 mCi to allow high quality images (Becker et al., 2006).

Giovanella et al (2011) predicted the effectiveness of radioiodine-131 ablation in patients with differentiated thyroid carcinoma by thyroid remnant estimation using Tc-99m pertechnetate scintigraphy post surgically. The study showed that the higher the Tc-99m pertechnetate uptake rate, the higher chance of unsuccessful ablation in patient with thyroid cancer especially in the uptake rate greater than 1.4%.

1.6 STAGING AND MANAGEMENT

There have been many staging systems proposed for well differentiated thyroid cancer, however, the tumour-node-metastasis (TNM) staging classification system is the most widely used and accepted. It is defined jointly by the Union International Contre le Cancer (UICC) and the American Joint Committee against Cancer (AJCC). These staging systems are based on histopathological description of the tumour sizes (T), lymph nodes involvement (N) and distant metastasis (M). The age at presentation is very important in this classification, especially whether patient is younger or older than 45 years at the initial presentation (Haugen et al., 2016, Cooper et al., 2009).

Group	T category	N category	M category
Papillary or follicular (differentiated)			
Under 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
45 years and older			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Figure 3: AJCC/UICC anatomical stage and prognostic group for papillary or follicular (differentiated) thyroid carcinoma. Adapted from AJCC cancer staging manual, edition (2010) published by springler science and Business Media LLC.

The AJCC/TNM staging system is not without flaws. It does not predict the risk of disease recurrence in differentiated thyroid carcinoma. In 2009, American Thyroid Association (ATA) thyroid cancer guidelines proposed a three tiered clinico-pathologic risk stratification system that classifies a patient as having low, intermediate or high risk of recurrence. This three tiered clinic-pathological risk stratification is revised in 2015 with a more detailed description as shown below (Haugen et al., 2016, Cooper et al., 2009) .

ATA Low risk	• No local or distant metastases. • All macroscopic tumours have been resected. • Intrathyroidal papillary thyroid ca with no evidence of extrathyroidal extension, vascular invasion or metastases. • Encapsulated follicular variant of papillary thyroid cancer. • Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal vascular invasion. • Intrathyrodal, papillary microcarcinoma, unifocal or multifocal. • No tumour invasion of loco-regional tissue or structures. • The tumour does not have aggressive histology. • If I-131 is given, there is no RAI avid metastatic focus outside the thyroid bed on first ablation. • No vascular invasion. • Clinical N0 or $\leq$ 5 pathological N1 micrometastases (<0.2 cm in diameter).
ATA Intermediate risk	• Microscopic invasion of tumour into perithyroidal soft tissue.

	• RAI avid metastatic foci in the neck on the first post treatment whole body RAI scan. • Aggressive histology (tall cell, hobnail variant, columnar cell carcinoma). • Intrathyroidal, papillary thyroid carcinoma, primary tumour 1- 4 cm V600E BRAF. • Multifocal papillary microcarcinoma with extrathyroidal extension. • Papillary thyroid cancer with vascular invasion. • Clinical N1 (all lymph node <3 cm in largest diameter).
ATA High risk	• Macroscopic invasion of tumour into perithyroidal soft tissue. • Incomplete tumour resection. • Distant metastasis. • Post-operative serum thyroglobulin suggestive of distant metastasis. • Follicular thyroid carcinoma with extensive vascular invasion (>4 foci of vascular invasion). • Clinical N1 (all lymph node >3cm in largest diameter).

Table 1.0 : 3 tiered clinic-pathologic risk stratification system adapted from (Haugen et al., 2016)

The basic goal of initial therapy for patients with differentiated thyroid carcinoma is to improve overall survival by reducing the risk of persistent disease or recurrence and associated morbidity. The primary treatment is by removing the primary tumour for newly diagnosed thyroid carcinoma. Near total or total thyroidectomy is the mainstay treatment for all patient in uncomplicated cases with differentiated thyroid carcinoma tumour size of more than 1 cm without any evidence of

local disease involvement, regional lymph nodes or distant metastasis (Haugen et al., 2016). Patients with cervical or mediastinal lymph nodes metastases require more extensive lymph nodes dissection as there is risk of disease persistent or recurrence (Sosa and Udelsman, 2006).

Serum thyroglobulin is supposed to be no detectable after total thyroidectomy because it only produced by thyroid cell or thyroid cancer cell. This is the reason why serum thyroglobulin is specific marker for thyroid carcinoma. Therefore the presence of serum thyroglobulin in the blood should raise suspicions of residual or recurrent thyroid cancer (Haugen et al., 2016, Kim et al., 2005). The sensitivity of serum thyroglobulin is very high by high serum TSH level (TSH $\geq$ 30 pmol/L). Patient start on L-thyroxine as a thyroid hormone replacement therapy and to supress the production of TSH, which can stimulate the growth of thyroid cancer cells after total thyroidectomy (Mazzaferri et al., 2003).

1.7 RADIOIODINE-131 (RAI) THERAPY

There is possibility of residual thyroid tissue remained that may harbour cancer cells following total thyroidectomy. In view of this, radioiodine-131 is recommended as adjunct treatment in patient post thyroidectomy with the aim to eliminate the remaining thyroid tissue and thyroid cancer cells. This therapy is also referred to as remnant ablation therapy (Van Nostrand, 2009).

Radioiodine-131 is a beta emitting radionuclide with a radioactive decay of about 8 days. It consists particles with a maximum energy of 0.61 MeV (average energy of 0.192 MeV) and a range in the tissue of 0.8 mm (Meier et al., 2002). The beta particle emitted by the radioisotope radioiodine-131 destroys the associated thyroid tissue with little damage to surrounding tissues (Lin, 2015). It emit gamma ray of 364 KeV (Meier et al., 2002) .

After oral ingestion, radioiodine-131 enters blood circulation and is ultimately taken up by the thyroid gland by iodide transporter and process similarly as natural iodine. The beta particle of radioiodine-131 deliver ionizing radiation that disrupts the chemical bonds within thyroid cells, causing devastating damage on DNA molecules, triggering cellular dysfunction and ultimately causing cell death (Elisei et al., 2013).

Utilising low doses 30 mCi ablation of thyroid tissue after near-total thyroidectomy had been proposed and recommended in patient with low risk well differentiated thyroid carcinoma (Ibrahim et al., 2016, Schlumberger et al., 2012). These studies had concluded that 30 mCi was as effective as larger doses in inducing ablation, and since it could be administered without hospitalizing the patients, was an appropriate treatment. It also minimizes radiation exposure, and damage to the salivary glands (Ibrahim et al., 2016, Schlumberger et al., 2012).

1.8 PATIENT PREPARATION AND IODINE RESTRICTED DIET

Well differentiated thyroid cancer cells are hypofunctional but still maintains the physiological ability to take up radioactive iodine at lesser degree compare to normal thyroid tissue (Ziessman et al., 2014). In view of this, high level of serum TSH is important for the effectiveness of radioiodine-131 treatments. It is recommended to achieve the minimum level of TSH > 30U/ml prior to the therapy to ensure good uptake (Meier et al., 2002). This makes any remaining thyroid cells become more readily to take up iodine and enhanced the efficiency of the thyroid tissue and thyroid cancer cells to take uptake radioiodine-131.

In order to stimulate serum TSH > 30 Ul/ml in patient post thyroidectomy, two methods have been utilized (Robbins et al., 2001, Borget et al., 2008). The first method is withholding thyroxine (T4) hormone for 4 to 6 week and triiodothyronine hormone (T3) for 2 week prior to radioiodine-131 therapy (Lee et al., 2010). In this method, serum TSH level is progressively increased at the expense of patient becoming hypothyroid. If the symptoms of hypothyroid are not tolerated by patient, alternatively patient is given recombinant TSH (also known as rhTSH or Thyrogen). This technique is also suitable for patients with existing medical problems such as heart failure, depression which do not allow them to stop thyroid replacement therapy (Schroeder et al., 2006). This rhTSH is administered via intramuscular injection of 0.9 mg on two consecutive days prior to radioidine-131 therapy (Borget et al., 2008, Robbins et al., 2001).

A temporary low iodine diet of at least 2 weeks is recommended before patients undergone radioidine-131 ablation therapy (Sawka et al., 2010). The rationale for a low iodine diet in such circumstances is to further deplete the iodine concentration in the body and optimize radioiodine-131 uptake in the thyroid cells. Patients are advised avoid food rich iodine content such as fish, shell fish, crab, and seaweed, followed by egg, milk, dairy products and fortified or iodized salt. Bread made with high iodinated dough conditioner, chocolate as well as dried and cure food product also contain high level of iodine that needs to be avoided.

1.9 AIM OF MANAGEMENT AND FOLLOW UP

The main aim of treating patients with low risk well differentiated thyroid carcinoma is to achieve total cure from the disease, improve overall survival, and reduce risk of persistent disease or recurrence after total thyroidectomy and radioiodine-131 ablation therapy. This management includes thyroid replacement therapy with L-thyroxine for TSH suppression along with biochemical and imaging surveillance. In the event of recurrence either locally or distantly during subsequent follow up, patients are required to refer back either for surgical intervention or repeated radioactive iodine ablation until a treatment effect is no longer viable or bone marrow reserve is compromised (Haugen et al., 2016).

For non resectable and non-radioiodine-131 responsive disease or dedifferentiated thyroid cancer, many other alternative therapies may be offer such as radiation therapy, investigational chemotherapy or tyrosine kinase inhibitor (TKIs) therapy (Haugen et al., 2016).

2.0 RATIONALE AND OBJECTIVE