RADIATION DOSE ASSESSMENT USING 3D QUANTITATIVE SPECT/CT IMAGING IN LOW RISK DIFFERENTIATED THYROID CANCER PATIENTS

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by

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LIST OF SYMBOLS

%	Percentage
<	Less than
>	More than
±	Plus minus
≤	Less than or equal to
^{123}I	Iodine-123
^{124}I	Iodine-124
^{131}I	Iodine-131
180°	180 degree
∞	Infinity
A	Activity concentration
Ã	Accumulated activity
A_0	Initial activity
Bq	Becqueral
Bq/cc	Becqueral per cubic centimeter
c	mean number of counts
cm	centimeter
$D(r_T)$	Dose to target organ
g	gram
g/dl	gram per decilitre
GBq	Giga becqueral
Gy	Gray
h	hour
J/kg	Joule per kilogram

kBq	kilo becqueral
keV	kilo electron volt
kg	kilogram
kV	kilovoltage
kVp	kilovoltage peak
mAs	miliampere seconds
MBq	Mega becqueral
mCi	miliCurie
mg/l	miligram per litre
mg/m^2	miligram per meter square
min	minute
mIU/l	mili International unit per litre
ml	mililitre
mm	milimeter
n	number of projections
ng/ml	nanogram per litre
r_S	Source organ
r_T	Target organ
s	second
t	time per projection
v	Voxel size
α	Alpha particle
β	Beta particle
γ	Gamma rays
μCi	microCurie
μCi/cc	microCurie per cubic centimeter
μg/l	microgram per litre

µl	microlitre
µSv/h	microSievert per hour
τ_{blood}	Blood residence time
$\tau_{total\ body}$	Total body residence time

LIST OF ABBREVIATIONS

2D	Two dimension
3D	Three dimension
AHASA	As high as safely administrable
AJCC	American Joint Committee on Cancer
ALARA	As low as reasonably achievable
ATA	American Thyroid Association
AUC	Area under the curve
BMI	Body mass index
CDR	Collimator detector response
CF	Calibration factor
cpm	Count per minute
CT	Computed Tomography
CTS	Counts
dpm	Disintegrations per minute
DTC	Differentiated Thyroid Cancer
DVH	Dose volume histogram
dxWBS	Diagnostic whole-body scan
EANM	European Association of Nuclear Medicine
EBRT	External beam radiation therapy
FBC	Full blood count
FBP	Filtered back projection
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FNA	Fine needle aspiration
FOV	Field of view
FTC	Follicular thyroid cancer
GM	Geiger Muller
HB	Hemoglobin
HCC	Hurthle cell cancer
HCT	Hematocrit
HE	High energy

HPE	Histopathology examination
ICRP	International Commission on Radiological Protection
IDAC	Internal Dose Assessed by Computer
LOI	Line of identity
MC	Monte Carlo
MIRD	Medical Internal Radiation Dose
MIRDOSE	Medical Internal Radiation Dose
MLEM	Maximum likelihood expectation maximization
MRI	Magnetic Resonance Imaging
MRT	Molecular radiation therapy
NaI(Tl)	Sodium iodide doped with Thallium
NTT	Near-total thyroidectomy
OLINDA/EXM	Organ Level Internal Dose Assessment/EXponential Modeling
OSEM	Ordered subset expectation maximization
P value	Probability value
PET/CT	Positron Emission Tomography / Computed Tomography
PLT	Platelet
PTC	Papillary thyroid cancer
PVC	Partial volume correction
PVE	Partial volume effect
RADAR	Radiation Dose Assessment Resource
RAI	Radioactive Iodine
RBC	Red blood cell
RC	Recovery coefficient
rhTSH	Recombinant human thyroid-stimulating hormone
ROI	Region of interest
RR	Resolution recovery
rxWBS	Post therapy whole-body scan
S value	Absorbed dose rate per unit activity
SOP	Standard operation procedure
SPECT	Single Photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
T3	Triiodothyronine
T4	Thyroxine

TAC	Time activity curve
TEW	Triple energy window
Tg	Thyroglobulin
THW	Thyroid hormone withdrawal
TNM	Tumour, node, metastasis
Tra	Thyoid hormone receptor alpha
TRb	Thyroid hormone receptor beta
TRH	Thyroid releasing hormone
TSH	Thyroid-stimulating hormone
TT	Total thyroidectomy
VOI	Volume of interest
VSF	Volume sensitivity factor
VSV	Voxel S value
WBC	White blood cell
WBS	Whole-body scan
WHO	World Health Organization

LIST OF APPENDICES

PENILAIAN DOS SINARAN MENGGUNAKAN PENGIMEJAN KUANTITATIF 3D SPECT/CT BAGI PESAKIT KANSER TIROID JENIS DIBEZAKAN BERISIKO RENDAH

ABSTRAK

Kelaziman kanser tiroid terus meningkat dengan meluas. Pembedahan, terapi radioiodin, kemoterapi, terapi hormon tiroid dan terapi sasaran adalah semua pilihan yang boleh digunakan untuk rawatan kanser tiroid, sama ada secara bersendirian atau gabungan. Kajian ini hanya akan merangkumi pesakit dengan kanser tiroid berisiko rendah daripada jenis kanser tiroid yang dibezakan secara khusus yang telah menjalani *total thyroidectomy* (TT). Pesakit ini telah dirujuk ke Jabatan Perubatan Nuklear di Hospital Pulau Pinang untuk terapi ablasi radioaktif iodin dan menerima 2960 MBq sehingga 3700 MBq aktiviti tetap. Penggunaan amalan aktiviti tetap menimbulkan cabaran dalam menilai sejauh mana aktiviti radioiodin akan mengakibatkan dos yang yang boleh membawa maut kepada organ normal atau dos yang boleh diterima yang boleh diserap oleh badan. Matlamat kajian adalah untuk menentukan dos sinaran individu kepada sisa tiroid dan organ terpilih seperti hati, limpa, buah pinggang, paru-paru, dan sumsum tulang berdasarkan prinsip *Medical Internal Radiation Dosimetry*. Teknik kuantitatif tiga dimensi (3D) digunakan untuk memperoleh peta ketumpatan khusus pesakit (daripada imej CT) dan peta aktiviti (daripada imej SPECT) bersama-sama dengan dosimetri darah menggunakan pengimejan *Single Positron Emission Computed Tomography* yang dikombinasikan dengan *Computed Tomography* (SPECT/ CT). Dosimetri darah dianggarkan menggunakan teknik OLINDA, IDAC, dan EANM. Keputusan telah menunjukkan bahawa OLINDA dan IDAC mempunyai tahap kesepakatan yang agak tinggi apabila mengira jumlah terapi radioiodin yang

akan diserap oleh sumsum tulang merah. Walau bagaimanapun, pendekatan EANM telah menunjukkan nilai dos yang diserap yang lebih besar (12.7%) kerana jisim dan *body count* pesakit perseorangan mempengaruhi anggaran dos yang diserap. Menggunakan pelbagai pendekatan untuk mengira dos yang diserap oleh organ dan tumor individu adalah salah satu fokus utama penyelidikan ini. Keputusan menggunakan OLINDA menunjukkan bahawa organ dengan isipadu yang besar, seperti hati dan paru-paru, memberikan bacaan yang menunjukkan nilai dos yang diserap yang dianggarkan berkurangan. Apabila digunakan pada kawasan dengan isipadu yang kecil, seperti tumor, nilainya dianggarkan berlebihan. Walau bagaimanapun, nilai dos organ dan tumor tidak berbeza antara aliran kerja MIM, tetapi terdapat perbezaan yang ketara apabila membandingkan OLINDA dan MIM yang menggunakan berbilang imej SPECT/CT. Keputusan ini memberikan sedikit gambaran tentang ketepatan anggaran dos yang diserap menggunakan MIM Sureplan MRT sebagai alat dosimetri yang mempunyai harapan, justeru membuka jalan untuk penyelidikan lanjut. Kajian pengesahan mesti dilakukan untuk menentukan sama ada dosimetri berasaskan voxel adalah lebih baik daripada dosimetri berasaskan organ, yang melibatkan membandingkan teknik berasaskan voxel dan berasaskan organ dengan pendekatan langsung Monte Carlo.

RADIATION DOSE ASSESSMENT USING 3D QUANTITATIVE SPECT/CT IMAGING IN LOW RISK DIFFERENTIATED THYROID CANCER PATIENTS

ABSTRACT

The prevalence of thyroid cancer continues to increase widely. Surgery, radioiodine therapy, chemotherapy, thyroid hormone therapy, and targeted therapy are all applicable options for the treatment of thyroid cancer, either alone or in combination. This study only include patients with low-risk thyroid cancer of a specifically differentiated thyroid cancer type who have undergone total thyroidectomy (TT). These patients were referred to the Nuclear Medicine Department at Penang Hospital for radioactive iodine ablation therapy and received 2960 MBq to 3700 MBq of fixed administration activity. The utilisation of the fixed activity practice poses a challenge in assessing the extent to which the radioiodine activity would result in a lethal dose to normal organs or a tolerable dose that can be assimilated by the body. Based on the Medical Internal Radiation Dosimetry principle, the study's aim is to determine the individual radiation dose to the thyroid remnant and selected organs such as the liver, spleen, kidney, lung, and bone marrow. A quantitative three-dimensional (3D) technique was used to acquire the patient specific density map (from CT image) and activity map (from SPECT image) in conjunction with blood dosimetry utilising Single Positron Emission Computed Tomography in combination with Computed Tomography (SPECT/CT) imaging. Blood dosimetry was estimated using OLINDA, IDAC, and EANM technique. The results have indicated that OLINDA and IDAC have a relatively high level of consensus when it comes to calculating the amount of radioiodine therapy that would be absorbed by the red bone marrow. The

EANM approach, however, has demonstrated a greater value of absorbed dose (12.7%) since the individual patient mass and body count influenced the absorbed dose estimation. Utilizing a variety of approaches to compute the absorbed dose by individual organs and tumours is one of the primary focuses of this research. The results of employing OLINDA demonstrate that organs with a large volume, such as the liver and lung, give readings that reflect underestimated values of the absorbed dose. When applied to areas with a small volume, such as tumours, the value is overestimated. However, the organs and tumours dose values did not vary between MIM workflows, but there was a significant difference when comparing OLINDA and MIM employing multiple SPECT/CTs images. These results provide some insight into the accuracy of absorbed dose estimation using MIM Sureplan MRT as a promising dosimetry tool, hence paving the way for further research. A validation study must be done to determine whether voxel-based dosimetry is preferable to organ-based dosimetry, which involves comparing the voxel-based and organ-based technique with the direct Monte Carlo approach.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Typically, thyroid cancer begins when abnormal changes and out-of-control cell growth occur in the thyroid gland. This results in forming a mass, which is referred to as a tumour, which can be either noncancerous or cancerous. There are four subtypes of thyroid cancer, and they are referred to as papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer. Differentiated thyroid cancer (DTC) is the most frequent type of thyroid cancer and comprises both papillary and follicular histology (Kakudo et al., 2018).

Thyroid cancer is generally treated with a single treatment or a combination of treatments, depending on its severity. Patients with DTC will mostly require surgery to remove a small section of their thyroid gland or the entire gland; a procedure called a near or total thyroidectomy, followed by radioactive iodine (RAI) treatment. Radiation-induced iodine therapy has been shown to be successful in treating DTC in individuals who have undergone thyroid surgery. Following the ingestion of a moderate dose of radioactive iodine ^{131}I, the iodine is absorbed into the bloodstream and concentrated in the thyroid gland, where it begins to damage the gland's cells.

This study was carried out on adult patients with DTC who have undergone total thyroidectomy (TT) or near-total thyroidectomy (NTT) and were referred to Nuclear Medicine Department, Penang Hospital, for radioactive iodine ablation treatment. However, the study excluded patients who have distant metastases that cannot be evaluated and cancer that has spread to other parts of the body, which will have a different effect on the dose burden of the other organs.

This study assessed the radiation burden on sensitive organs such as the liver, kidney, spleen, bone marrow, and lung when patients received RAI therapy using the standard fixed activity approach. As part of the study, a quantitative three-dimensional (3D) approach has been adopted using Single Positron Emission Computed Tomography in combination with Computed Tomography (SPECT/CT) imaging in conjunction with blood dosimetry based on the Medical Internal Radiation Dose (MIRD) principle to assess the variation in absorbed dose. In addition, planar imaging of the patients obtained to quantify the variations in absorbed dose between 3D SPECT/CT and planar scintigraphy.

1.2 Problem statement

The effectiveness of the quantity of ^{131}I activity administered to patients in a single oral ^{131}I administration has been a long-standing source of debate in the field of radioactive iodine therapy. Basically, there are three fundamental approaches to ^{131}I therapy: empirical fixed administered activity, blood-based dosimetry, and lesion-based dosimetry. When utilising the fixed activity technique, it can be difficult to determine whether the radioiodine activity will provide a lethal dose to other organs or a reasonably safe dose to be absorbed by the body. According to one of the study, administering 100 – 300 mCi ^{131}I empirically to certain patients may result in a theoretical increase of 2 Gy of absorbed dose to the bone marrow (Kulkarni et al., 2006). The possibility of radiation risk must be considered, even if numerous studies (Fallahi et al., 2012; Kukulska et al., 2010) have shown that increasing the amount of activity given to patients will also improve the success rate of residual ablation. The correlation between high activity or low activity with the radiation burden on other organs is still unclear.

1.3 The rationale of the study

To date, no randomised trial has been conducted to investigate the most effective therapeutic approach. According to the research that compares the effectiveness of dosimetric and empiric approaches, individuals with locoregional disease exhibit a higher probability of positive response subsequent to dosimetric intervention as opposed to empiric therapy (Klubo-Gwiezdzinska et al., 2011). Dosimetric maximal activity administration has been shown in one trial to be more effective than empiric dose failure (Lee et al., 2008). This study emphasises the variability that arises from utilising diverse techniques to measure the absorbed doses of organs and tumours.

1.4 Objectives of the study

1.4.1 General objective

To assess the individual radiation dose to the thyroid remnant and sensitive organs such as liver, spleen, kidney, lung and bone marrow using 3D SPECT/CT based on the Medical Internal Radiation Dosimetry principle.

1.4.2 Specific objectives

1. To determine the accuracy of activity quantification in SPECT/CT camera and NaI(Tl) well counter over a range of activities and time.
2. To examine the accuracy of dose estimation to red bone marrow utilizing blood-based methods in three different tools; OLINDA/EXM 2.0, IDAC-Dose 2.1, and EANM SOP for ^{131}I dosimetry.
3. To determine whether the initial RAI ablation dose affected the peripheral full blood count (FBC) in patients with low-risk differentiated thyroid cancer (DTC).

4. To compare different methodologies for absorbed dose calculation and evaluate the efficacy of the post-therapeutic dosimetry utilising quantitative SPECT imaging.

1.5 Significance of the study

The study is looking into the method to quantify the ^{131}I activity and estimate the absorbed dose in thyroid cancer patients in order to perform patient-specific dosimetry using 3D SPECT/CT. The study's findings demonstrate its originality and substantial impact on the existing corpus of knowledge, specifically within the area of internal dosimetry. The primary finding of this research underscores the variability that arises from utilising differing techniques for quantifying the absorbed doses of organs and tumours.

1.6 Scope of the study

This study focuses on low-risk, differentiated thyroid cancer patients who have undergone surgery to remove the entire thyroid gland and have been given a fixed activity of RAI therapy for further treatment. Figure 1.1 displays a diagrammatic representation in yellow that highlights the scope of the thesis. Several techniques were utilised in order to determine the amount of radiation that was taken in by the bone marrow as well as by the other organs. The assessment of the therapy's efficacy was conducted by analysing the findings of a comprehensive diagnostic whole-body scan and measuring the serum Tg level. Multiple dosimetry software were utilised in the study. Table 1.1 provides a comprehensive summary of the various dosimetry methods.

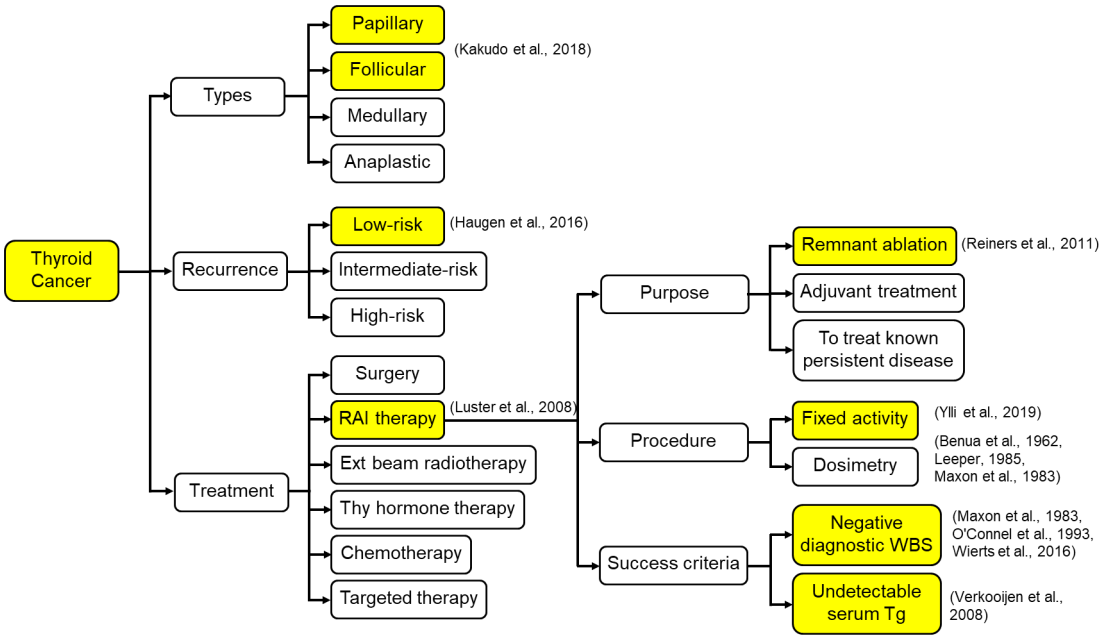

Figure 1.1 A diagrammatic representation of the scope of the thesis has been highlighted in yellow.

Table 1.1 Overview of dosimetry method.

Method	**OLINDA**	**IDAC**	**MIM**
Availability	Commercial dosimetry software.	Free research software.	Commercial dosimetry software.
Dose calculation model	Employing a RADAR group-developed voxel-based computational phantom.	Using the ICRP 110 adult computational voxel phantom.	Utilising a patient-specific dosimetry (not model-based).
Approval body	FDA approval.	No approval.	FDA approval.
Absorbed dose calculation	Uniform activity distributions.	Uniform activity distributions.	Non-uniform activity distributions.

1.7 Outline of the thesis

This thesis is structured into ten chapters. The following is an outline of the thesis's framework.

Chapter 1 gives a short summary of the problem and what the thesis aims to do. Chapter 2 provides an overview of the fundamental aspects of the thyroid gland, including the mechanisms underlying the transformation of normal thyroid tissue into cancerous tissue. Additionally, the chapter briefly outlines the various types of thyroid cancer and the corresponding approaches to treatment. Subsequent to this, the present chapter will focus upon the function of SPECT/CT in radioiodine therapy, along with its significance in the computation of internal dose. Chapter 3 explained upon the overall methodology employed in the research. Chapter 4 investigates the quantification accuracy of SPECT and planar imaging. This chapter also investigates the cross-calibration between the dose calibrator and the well counter. This chapter highlights on the thresholding technique utilised for image segmentation. Chapter 5 explores the various techniques utilised in the estimation of absorbed dose in bone marrow. Chapter 6 of the study examines whether the initial RAI ablation had an impact on the peripheral FBC. Comparisons of different techniques for estimating the dose at the organ and voxel levels have been addressed in Chapter 7. Chapter 8 and 9 contain the overall discussion and conclusion of the study. Chapter 10 of the study has comprehensively discussed the limitations of the research and provided recommendations for future studies.

CHAPTER 2

LITERATURE REVIEW

2.1 Thyroid gland

The thyroid is an endocrine gland situated in the anterior neck's lower region, inferior to the larynx, between the second and third rings of the trachea. It comprises two lobes, one on each side (right and left) of the tracheal wall and one isthmus that binds them together. On average, each lobe is 4 cm in length, 2 cm in width, and 2 – 3 cm in thickness.

The thyroid gland has developed to save and store iodine in humans and most animals. Iodinated molecules, iodotyrosines, and iodothyronines are produced by the thyroid, the latter of which contains thyroid hormones. Iodine is found in various foods, including dairy products, grains, and meat. The thyroid and kidneys are the two organs that require the most iodine (Benvenga, Tuccari, Ieni, & Vita, 2014).

The hypothalamus, the anterior pituitary gland, and the thyroid gland make up the components of a self-regulating circuit known as the hypothalamic-pituitary-thyroid axis. The principal regulator of thyroid function is thyroid-stimulating hormone (TSH), a peptide hormone generated in the anterior pituitary gland. TSH is influenced by both thyrotropin-releasing hormone (TRH) produced in the hypothalamus and thyroid hormone levels in the blood. Thyroid hormones suppress TRH synthesis. As a result, there is a reduction in TSH release from the pituitary gland and a decrease in the synthesis and release of thyroid hormones.

The thyroid gland produces two primary hormones: thyroxine (T4) and triiodothyronine (T3), with T4 being the primary product (about 90%). Most T3 is synthesised from T4 via deiodination in peripheral tissues such as the liver, kidneys, and muscle, catalysed by deiodinases.

Thyroid hormone has both genomic and non-genomic effects on the peripheral nervous system. They were formerly assumed to work by attaching to and activating certain nuclear receptors, which then changed the expression of target genes (genomic actions of thyroid hormone). The thyroid hormone receptor is divided into two isoforms (alpha and beta) encoded by particular genes on particular chromosomes. The majority of thyroid hormone receptor alpha (TRa) components are located in the bone, the heart, and the brain. TRb1, which stands for thyroid hormone receptor beta, may be found in the liver, the kidneys, and the thyroid. TRb2, on the other hand, is mostly located in the retina, the cochlea, and the pituitary gland.

2.1.1 The function of thyroid hormones

Thyroid hormones regulate metabolism, growth, and many other body functions. They are frequently referred to as metabolic hormones because the levels of these hormones influence the basal metabolic rate of the body, which is the amount of energy that is utilised by the body when it is at rest.

Thyroid hormones are inherently caloric, resulting in increased oxygen demand and contribute to the production of body heat. They stimulate protein catabolism, gluconeogenesis, glucose utilisation, and lipid metabolism. Thyroid hormones affect cardiac function by raising heart rate, myocardial contractility, blood volume, and cardiac output while reducing peripheral vascular volume. To promote bone formation and growth, they increase the production of cytokines, growth factors, and other substances. Due to their ability to induce cell differentiation, proliferation, and maturation, thyroid hormones are critical for foetal growth and brain development in the initial weeks of life.

2.1.2 Pathophysiology

2.1.2(a) Hyperthyroidism

Hyperthyroidism is a high metabolic state caused by excessive T4 and T3 production. Heat sensitivity, weight loss, anxiety, hyperreflexia, diarrhoea, and palpitations are all common symptoms of hyperthyroidism. The most prevalent symptoms are caused by increased stimulation of the basal metabolic rate, thermogenesis, resting heart rate, cardiac output, and the central and peripheral neurological systems.

The most prevalent cause of hyperthyroidism is Graves disease. It is an autoimmune disorder caused by the development of TSH receptor antibodies, which increase thyroid gland development and hormone release. Patients will have excessively high T4 and T3 levels and a drop in TSH. Multinodular goitre, single thyroid adenoma, thyroiditis, iodide- or drug-induced hyperthyroidism, and, in rare cases, a TSH-secreting pituitary tumour also causes hyperthyroidism.

2.1.2(b) Hypothyroidism

Hypothyroidism is a state of low metabolic activity caused by a lack of T4 and T3 hormones. Cold intolerance and weight gain are common symptoms of hypothyroidism, caused by a decrease in basal metabolic rate and thermogenesis. Other symptoms include misery, lethargy, reduced peripheral reflexes, and constipation caused by impaired central and peripheral nervous system stimulation.

In iodine-sufficient regions, the most prevalent cause of hypothyroidism is Hashimoto's Thyroiditis. It is a condition caused by the thyroid gland being destroyed by an autoimmune reaction. Depending on the level of fibrosis, the thyroid gland may grow to normal size or shrink.

2.1.3 Thyroid Nodule

According to American Thyroid Association (ATA), a thyroid nodule (solitary, multiple, cystic, or solid) is defined as a localised tumour within the thyroid gland (Haugen et al., 2016). Thyroid fine needle aspiration (FNA) is a well-established method for determining the presence of thyroid nodules prior to surgery. 70–75% of thyroid nodules are classified as benign or malignant with remarkable accuracy by cytology evaluation of FNA samples (Wartofsky & van Nostrand, 2017). The major goal of thyroid FNA is to distinguish individuals at high surgical risk and avoid unnecessary surgery for benign diseases.

2.1.4 Thyroid Cancer

Thyroid cancer is significant because it is one of the top ten malignancies among women and because it is detectable in an early stage, precise and specialised treatment, and great survival rates (Wartofsky & van Nostrand, 2017).

The prognosis for papillary carcinoma is superior to that of anaplastic carcinoma. Patients under the age of 40 had a higher rate of survival than those beyond the age of 40. However, evaluating risk is difficult because people under the age of 40 have low cancer death rates but high tumour recurrence rates (Othman, Abd Ghani, & Mohd, 2018).

The thyroid gland has different histology; therefore, distinguishing between benign and malignant thyroid tissue is essential. True follicular carcinomas account for just 10–15% of all thyroid malignancies, despite the fact that the majority of primary thyroidal tumours start from the follicular epithelium (Dralle et al., 2015).

Follicular thyroid carcinoma (FTC) is more rarely often multicentric than papillary thyroid carcinoma (PTC), and the diagnostic distinction between FTC and PTC is based on their appearance on cytologic examination.

Most patients with differentiated thyroid cancer are advised by their physicians to have their thyroid organ removed to prepare for radioiodine therapy. Regardless of the degree of thyroidectomy, the incidence of complications is lowest among surgeons with the most expertise (Hauch, Al-Qurayshi, Randolph, & Kandil, 2014).

2.1.4(a) Papillary Thyroid Cancer

The most prevalent endocrine cancer is papillary thyroid cancer, which is typically linked with a favourable prognosis. PTC is a type of thyroid follicular epithelial cancer that, like follicular carcinoma, has the highest degree of differentiation.

In addition to the conventional type of PTC, 14 variants were listed in the 2017 World Health Organization (WHO) classification of thyroid tumours. There is a wide range of variation in the occurrence of these variations across patient populations, but papillary microcarcinoma, encapsulated, follicular and tall cell variants are seen more frequently than other varieties, on average (Kakudo et al., 2018).

PTC has the greatest prognosis of all the types of thyroid cancer and is typically diagnosed in people in their third or fourth decades of life. However, it must be mindful that even with young patients with no distant metastasis, PTCs with significant lymph node metastases necessitate extensive initial surgery, thorough postoperative monitoring, and prompt and vigorous treatments for recurrent tumours (Ito et al., 2018).

Different papillary thyroid cancer variants may exhibit more aggressive behaviour than the original forms. Approximately 10 to 15% of individuals with more aggressive forms of papillary thyroid carcinoma, such as tall cell, columnar cell, solid variant, or the more newly identified hobnail variant, may experience recurrence, metastases, and cancer mortality (Asioli, Erickson, Righi, & Lloyd, 2013).

The most significant predictive factor for overall survival was older age, showing that PTC is often affluent, and that overtreatment should be avoided in many

circumstances. For elderly patients with PTC who lack high-risk characteristics, death from carcinoma is uncommon (Ito et al., 2020). If they are otherwise healthy and have a good performance status, high-risk elderly people should be evaluated for active therapy.

2.1.4(b) Follicular Thyroid Cancer

According to the invasion pattern, FTC was traditionally divided into two prognostic subgroups, minimally invasive or widely invasive. The new 2017 WHO Classification of Tumours has divided FTC into three prognostic categories, minimally invasive (capsular invasion only), encapsulated angioinvasive and widely invasive (Kakudo et al., 2018).

The diagnosis of FTC was based on the postoperative pathology reportWhen confronted with a follicular thyroid tumour, many patients still require a partial or total thyroidectomy for a clear diagnosis, despite the introduction of more recent molecular markers from thyroid FNA specimens (Nicolson et al., 2018).

Patients with follicular thyroid cancer often have a worse prognosis than those with papillary thyroid cancer (Giorgio Grani, Lamartina, Durante, Filetti, & Cooper, 2018), particularly in older patients and those with advanced tumours. In contrast to papillary subtypes, which are more prone to spread via lymphatics, follicular thyroid tumours tend to spread hematogenously to the lung, bone, liver, brain, and kidney (Madani, Jozaghi, Tabah, How, & Mitmaker, 2015).

Although PTC and FTC are both frequently referred to as differentiated thyroid cancers (DTC), FTC frequently exhibits biological characteristics that are different from PTC in terms of prognostic variables related to tumour recurrence and survival.

2.1.4(c) Hürthle Cell Cancer

Hürthle cell carcinoma is typically thought of as a subtype of follicular thyroid cancer. The most recent version of the WHO classification of tumours recognises Hürthle cell carcinoma and follicular thyroid cancer as independent entities due to data demonstrating a difference in biological behaviour and distinct genetic changes (Kakudo et al., 2018).

While both FTC and HCC originate in the follicular cell, the considerable disparity in oncogene expression between the two suggests that they should be treated as distinct diseases (Kure & Ohashi, 2021). Hürthle cells are only identifiable through fine needle aspiration cytology biopsies or histological examinations performed after surgery. While broadly invasive HCC exhibits substantial capsular invasion and/or vascular invasion of four foci or more, minimally invasive HCC refers to encapsulated tumours with microscopically discernible foci and a capsular or vascular invasion of less than four foci (Kure & Ohashi, 2021).

There is currently no agreement on the best way to treat HCC, and the effects of radioactive iodine treatment after surgery are not really clear because HCC has less iodine uptake, which makes it less responsive to RAI therapies (Kure & Ohashi, 2021).

2.1.4(d) Thyroid Cancer Staging

The "TNM" categorization system, established by the American Joint Commission on Cancer (AJCC), is one of the most widely used staging systems, and it is utilised by pathologists for most malignancies, including thyroid cancer.

This approach was developed to forecast the survival rate of cancer patients, however it is not useful for predicting whether or not the cancer will return following therapy for thyroid cancer. The 2017 publication of the 8th edition of the AJCC TNM staging system sought to enhance survival prediction for thyroid cancer patients over

the 2010 7th edition. Table 2.1 showing the TNM staging using 8th edition of AJCC staging system.

The age-at-diagnosis cut-off used for staging extended from 45 to 55 years in the AJCC 8th edition, which is one of the significant alterations pertaining to differentiated thyroid cancer. Patients with DTC were significantly down-staged by the 8th edition AJCC staging system, leading to improved recurrence and survival prediction compared to the prior staging method (Nam et al., 2018).

Table 2.1 TNM staging using AJCC staging system

AJCC stage	**Age at diagnosis (years)**	**Stage grouping**	**Description**
I	< 55	Any T Any N M0	Any tumour sizes It might or might not have spread to nearby lymph nodes. No distant metastasis
	> 55	T1 N0 or NX M0	Tumour ≤ 2 cm in greatest dimension limited to the thyroid. It has not spread to nearby lymph nodes No distant metastasis
	> 55	T2 N0 or NX M0	Tumour> 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid. It has not spread to nearby lymph nodes No distant metastasis
II	< 55	Any T Any N M1	Any tumour sizes It might or might not have spread to nearby lymph nodes. Distant metastasis is present

	> 55	T1 N1 M0	Tumour ≤ 2 cm in greatest dimension limited to the thyroid. It has spread to nearby lymph nodes No distant metastasis
	> 55	T2 N1 M0	Tumour> 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid. It has spread to nearby lymph nodes No distant metastasis
	> 55	T3a or T3b Any N M0	Tumour> 4 cm but confined to the thyroid (T3a), or it has grown into the strap muscles around the thyroid (T3b). It might or might not have spread to nearby lymph nodes No distant metastasis
III	> 55	T4a Any N M0	Any tumour size and has grown extensively beyond the thyroid gland into nearby tissues of the neck, such as the larynx, trachea, oesophagus, or the nerve to the larynx. It might or might not have spread to nearby lymph nodes No distant metastasis
IVA	> 55	T4b Any N	Any tumour size and has grown

		M0	extensively beyond the thyroid gland back toward the spine or into nearby large blood vessels. It might or might not have spread to nearby lymph nodes No distant metastasis
IVB	> 55	Any T Any N M1	Any tumour sizes It might or might not have spread to nearby lymph nodes Distant metastasis is present

The ATA established a system for stratifying patients' risk of recurrence based on their postoperative status. Patients were classified as low risk, intermediate risk, or high risk for recurrence.

Patients are classified as low-risk if they have had all visible tumours surgically removed, there is no local tumour invasion, no positive lymph node, and no distant metastases. They also do not have any histologies linked to aggressive clinical behaviour, such as tall-cell, insular, or columnar variants. Moreover, if radioiodine (RAI) ablation were to be administered for any reason, even though it is not often indicated for low-risk patients, no extrathyroidal uptake would be expected to be shown on a scan taken after treatment (Haugen et al., 2016).

Patients with positive lymph node metastases, vascular invasion, or one of the aggressive histologies would be considered intermediate-risk. On a post-therapy isotope scan, there is additional evidence of local invasion into perithyroidal soft tissues, as well as uptake detected external to the thyroid bed (Haugen et al., 2016).

Patients at high risk of recurrence have macroscopic tumours left by surgeons, distant metastases, or the probability of more extensive or severe disease based on extremely high serum thyroglobulin levels (Haugen et al., 2016).

There is no recommendation for ^{131}I residual ablation in patients at very low risk. Patients are considered to be in this category if the size of their tumour is less than one centimetre, there is no evidence of tumour invasion, clear margins, negative lymph node status, and there is no histology that is linked to a more aggressive behaviour (Wartofsky & van Nostrand, 2017).

2.1.5 Thyroid Function Test

A blood test called a thyroid function test is used to check the levels of thyroid hormones in the blood. This test may include thyroid-stimulating hormone (TSH), T4, T3, and thyroid antibody tests. Alterations to the TSH can serve as an early monitoring system, as they frequently occur before the actual level of thyroid hormones in the body becomes excessively high or excessively low.

Abnormal levels could mean that the patient may have an overactive thyroid or an underactive thyroid rather than cancer. Important to know is that thyroid function tests do not always indicate the presence of thyroid cancer and that the majority of people who have thyroid cancer have normal thyroid function.

2.1.5(a) Role of Thyroglobulin in Thyroid Cancer

Thyroglobulin (Tg) is a protein made by the thyroid gland. Patients with differentiated thyroid cancer should have their serum Tg levels checked regularly because they can offer crucial details regarding the existence or absence of metastatic, recurring, or residual disease. These measurements are useful in the initial diagnosis as well as post-surgical management and follow-up.

Thyroid cancer metastases and neck masses of thyroid origin can be identified via immunostaining of tissue for Tg in the primary diagnosis stage. There is a possible correlation between preoperative serum Tg concentrations and tumour mass in patients who have been diagnosed with differentiated thyroid cancer (Rasmussen et al., 2002).

Long-term follow-up of patients with DTC is aided greatly by the serum Tg value measured after surgery, as it is a strong prognostic indicator used to direct clinical therapy (Prpić, Franceschi, Romić, Jukić, & Kusić, 2018). It is possible to determine whether or not the surgery was successful by comparing the preoperative and postoperative serum Tg values (Indrasena, 2017). Complete tumour ablation in a low-risk patient is indicated by a Tg that stays undetectable (<1 μg/l) after either thyroid hormone withdrawal (THW) or recombinant TSH (rhTSH) stimulation. A detectable baseline serum Tg concentration with a large TSH response suggests the presence of normal thyroid tissue or well-differentiated cancer tissue that responds to TSH suppression.

Serum Tg levels are effective for early recurrence prediction, therapy efficacy, and disease progression monitoring in patients with DTC who have received sufficient treatment with surgery alone or combined with RAI therapy. While a decline in Tg level implies tumour shrinkage, an increase in Tg level indicates tumour recurrence or the existence of metastases.

Thyroglobulin (Tg) values obtained in the presence of anti-Tg antibodies may not be clinically reliable and cannot be used as a marker to detect persistent or recurrent disease after thyroidectomy and ablation of residual normal thyroid tissue. Because anti-Tg antibodies can have a major impact on the measurement of serum Tg, all laboratories that measure serum Tg should test for anti-Tg antibodies in any serum sample submitted for Tg assay (Frederik A Verburg et al., 2013).

2.1.6 Thyroid Remnant

Total thyroidectomy for thyroid cancer should be performed meticulously extracapsular, with all normal thyroid tissue removed. Due to minor portions of normal thyroid tissue purposely left behind to save crucial integrally associated neurological systems and some thyroid tissue that the surgeon may be unaware of, excision of all normal thyroid tissue may not be feasible in all cases (Zeuren et al., 2015). Any thyroid tissue activity identified on thyroid scintigraphy in the thyroid bed following thyroidectomy is referred to as thyroid remnant.

2.1.7 Diagnosis and Treatment of DTC

2.1.7(a) Surgery in the Management of Differentiated Thyroid Cancer

Surgical treatment should meet certain requirements in order to guarantee a decent quality of life, including being as radical as feasible, eradicating all cancer foci, tending to obtain a final cure, and gaining a low rate of both local recurrence and metastases (Conzo et al., 2014). Total tumour excision, reduced postoperative complications, and adequate pathology specimens for staging are all objectives of surgical intervention.

The recurrent laryngeal nerve and postoperative hypocalcemia are the two problems that are most frequently associated with thyroidectomies. These issues can have a significant impact on patients' quality of life and may be temporary or permanent. Consequently, it is essential to conduct a thorough preoperative evaluation to establish a baseline and analyse potential risk factors (Wang & Sosa, 2018).

Total thyroidectomy enables the use of radioactive iodine for adjuvant therapy, serum thyroglobulin for monitoring, and neck ultrasound to identify residual or recurrent disease. For individuals with modest tumours (<1 cm) restricted to one thyroid lobe and no nodules in the contralateral lobe, however, thyroid lobectomy is a viable

choice (Burns & Zeiger, 2010). Long-term survival is unaffected, despite research suggesting that lobectomy rather than thyroidectomy increases recurrence rates (Gemsenjäger et al., 2003).

Thyroidectomy is advised for FTCs with extensive vascular involvement and widespread invasiveness. Thyroidectomy is also advised for patients with PTCs of any size that have spread beyond the thyroid or are macroscopically invasive (Schmidbauer, Menhart, Hellwig, & Grosse, 2017). Due to the greater incidence of postoperative complications, TT should be chosen for intermediate-risk micro- and macro-DTCs to obtain a beneficial outcome (Colombo et al., 2021).

2.1.7(b) Radioiodine Therapy

Radioiodine therapy has been established since 1946 (Mayson, Chan, & Haugen, 2021). Radioiodine therapy is generically for remnant ablation, adjuvant treatment, or treatment of known locoregional or distant metastases.

RAI was shown to be beneficial for DTC patients who had a high likelihood of recurrence. RAI may be used to enhance surveillance after complete thyroidectomy, but it has not been shown to lower the chance of cancer recurrence in individuals at low risk who have tumours smaller than 1 cm in size without high-risk pathologic characteristics. There is no evidence from prospective clinical studies that RIT improves tumor-free and overall survival in patients with very low-risk DTC (Schmidbauer et al., 2017). Therefore, radioiodine therapy after surgery should be carefully applied.

Patients treated with high cumulative ^{131}I activity (>15 GBq) have been proven to experience significant carcinogenic consequences (Pacini et al., 2005). It is imperative to make every effort to utilise radioiodine only in patients who can benefit from it and when ^{131}I is indicated due to the linear association between the cumulative

administered activity of ^{131}I and the risk of subsequent leukaemia or other cancers (Rubino et al., 2003).

2.1.7(c) External Beam Radiotherapy

For patients with substantial residual disease who are unlikely to react to radioactive iodine and are not susceptible to additional surgery, conventional radiotherapy is advised (Burns & Zeiger, 2010). This strategy should be taken into consideration for high-risk patients who have a gross extrathyroidal extension.

Among the treatment choices for patients with thyroid cancer that has spread to the bones is external beam radiation therapy (EBRT) (Luster et al., 2008). The purpose of EBRT is to reduce bone lesion-related pain and neurological consequences. Although there is limited information on the effectiveness of EBRT in the treatment of thyroid cancer and bone metastases, it is believed that palliative EBRT relieves pain in 70% of patients (Wartofsky & van Nostrand, 2017).

Radiation treatment through external beam is often reserved for use as a last choice, after other treatment options like as surgery and radioactive iodine have been depleted (Schneider & Chen, 2013). Given that it is a local therapy, its benefits would only be anticipated in cases where there is a significant likelihood of local recurrence. This typically denotes situations in which patients with extrathyroidal extension have persistent disease following surgical resection (Wartofsky & van Nostrand, 2017). Patients with high-risk DTC who have undergone curative surgery and RAI may benefit from postoperative radiation therapy in order to improve their locoregional control (Jacomina et al., 2020).

2.1.7(d) Thyroid Hormone Therapy

After a thyroidectomy, euthyroidism must be restored, and normal serum levels of thyroid-stimulating hormone (TSH) must be maintained with thyroid hormone

therapy, typically with levothyroxine. On the presumption that thyroid cancer cells would develop and spread more slowly in the presence of subnormal serum levels of TSH, TSH suppression was suggested as a treatment approach (G. Grani, Ramundo, Verrienti, Sponziello, & Durante, 2019).

TSH should be kept between 0.5 and 2.0 mIU/l in patients with low-risk diseases or who have recovered from diseases, and 0.1 to 0.5 mIU/l for patients with high-risk diseases for a period of 5 to 10 years (Haugen et al., 2016). Levothyroxine medication may not be necessary for patients with normal serum TSH levels following surgery, and TSH suppression is not essential (G. Grani et al., 2019).

Bone mineral density at the hip was shown to be lower in women who underwent TSH suppression medication for DTC, however this effect was limited to those who had already gone through menopause (Yoon, Lee, Oh, Kim, & Lee, 2019). The administration of TSH suppressive medication has been linked to an increased risk of cardiovascular disease, and it has been shown to raise heart rate and left ventricular mass over the long run (Freudenthal & Williams, 2017).

After 9-12 months, a measurement of stimulated thyroglobulin can help determine whether or not long-term TSH suppression is necessary. Patients no longer need TSH suppression, although the TSH concentration should be kept at less than 2.0 mIU/l in those with stimulated thyroglobulin of less than 0.1 mg/l and neck ultrasounds that are negative for recurrence (Hovens et al., 2007).

2.1.7(e) Chemotherapy

It has been determined that cytotoxic chemotherapy plays no part in the usual care of DTC (Luster et al., 2008). Systemic cytotoxic chemotherapy is restricted for patients with rapidly advancing metastatic disease that is not suited or responsive to

surgery, radioiodine, and external beam radiotherapy and those who cannot enter clinical trials or employ targeted medicines (Busaidy & Cabanillas, 2012).

Following surgery or in cases when the tumour cannot be removed, chemotherapy is a crucial part of treatment for patients with a high disease burden, anaplastic malignancies, or poorly differentiated, non-iodine-avid tumours (Schneider & Chen, 2013). Doxorubicin, which received FDA approval and has a dose of 60 to 75 mg/m^2 every three to four weeks, is still the most effective conventional drug, but response rates are low (Sherman, 2010).

2.1.7(f) Targeted Therapy

In cancer treatment, targeted therapy refers to the employment of medicines or other substances to detect and destroy specific types of cancer cells. Even though targeted therapy drugs, like other cancer-fighting medications, are technically classified as chemotherapy, targeted therapy drugs do not function in the same way as conventional or standard chemotherapy therapies. In many cases, targeted drugs function by preventing cancer cells from replicating themselves. This implies that they can help prevent a cancer cell from dividing and producing new cancer cells, whereas standard chemotherapy, on the other hand, kills cancer cells that have already been produced.

Since these medications have a targeted impact, they only affect cancer cells and leave most normal, healthy cells unaffected by them. Compared to typical chemotherapy, it is cytotoxic to the majority of cells, meaning that it can harm normal, healthy cells and cancer cells.

Antibodies (anti-vascular endothelial growth factor) and small molecule tyrosine kinase inhibitors (such as sorafenib) should be evaluated in the context of ongoing clinical trials in this area. DTC patients with RAI-refractory metastases are

now eligible to receive tyrosine kinase inhibitors, such as sorafenib and lenvatinib, indicating that this is one potential therapeutic strategy for PTC recurrence in older patients (Brose, Worden, Newbold, Guo, & Hurria, 2017).

2.2 Radioiodine Therapy for Differentiated Thyroid Cancer

Radioiodine therapy is the routine procedure for differentiated thyroid cancer (DTC) patients following total thyroidectomy (Hong & Ahn, 2018; Luster et al., 2008). RAI therapy has three primary goals in patients with DTC following total thyroidectomy: ablation of the thyroid remnant, adjuvant therapy, and treatment of known disease.

In the case of all DTC patients who meet any of the following criteria, the American Thyroid Association recommends radioiodine therapy: distant metastases, extrathyroidal expansion of the tumour regardless of tumour size, or an initial tumour size more than 4 cm despite the absence of any other high-risk factors. Radioiodine therapy is also suggested for patients with 1-4 cm thyroid tumours localised to the thyroid and have proven lymph node metastases or other higher risk factors.

However, radioiodine therapy is not suggested for patients with unifocal cancer less than 1 cm in diameter without additional higher-risk criteria or for patients with multifocal cancer with all foci less than 1 cm in diameter in the absence of other higher-risk criteria (Haugen et al., 2016).

2.2.1 The Objectives of Radioiodine Therapy

Radiation therapy, particularly ^{131}I therapy for DTC, has two primary purposes. The first purpose is to provide the target with an adequate amount of radiation doses in such a way that the desired result, whether it is a cure, stabilisation, or palliation. The