THE INCREMENTAL VALUE OF
I-131 SPECT/CT OF THE NECK
IN THE MANAGEMENT OF
DIFFERENTIATED THYROID CARCINOMA

By

DR FATIN HAYYANI BINTI MOHAMAD NAJIB

Dissertation Submitted In Partial Fulfilment Of The Requirements For The Degree of Master Of Medicine (NUCLEAR MEDICINE)

ADVANCED MEDICAL AND DENTAL INSTITUTE
UNIVERSITI SAINS MALAYSIA

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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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FATIN HAYYANI BINTI MOHAMAD NAJIB

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Table of Contents

List of tables

List of figures

List of images

List of Abbreviations

AJCC	American Joint Committee on Cancer.
DTC	Differentiated thyroid carcinoma
DxWBS	Diagnostic planar WBS; it is a nuclear medicine imaging procedure after the DTC patient is being given I-131 for diagnostic purpose.
I-131	Iodine-131; radioactive iodine; radioiodine; a radioactive material given to DTC patient either for treatment or diagnostic purpose.
NIS	Sodium iodide symporter.
Planar WBS	Planar Scintigraphy; it is a two-dimensional nuclear medicine imaging, wherein I-131 are taken by the patient and the emitted radiation from the iodine-131 is detected and captured by gamma camera; usually captured as whole body scan (WBS).
RAI	radioactive iodine; radioiodine; Iodine-131; a radioactive material given to DTC patient either for treatment or diagnostic purpose.
RxWBS	Post therapy planar WBS; it is a nuclear medicine imaging procedure after the DTC patient being given I-131 for therapeutic purpose.
serum TSH	Serum thyroid stimulating hormone
SPECT/CT	Single-photon emission computed tomography/ computed tomography. It is a nuclear medicine tomographic gamma

imaging technique integrated with CT scanning for anatomical correlation.

WBS Whole body scan

Abstrak

Penambahan nilai klinikal oleh I-131 SPECT/CT leher dalam rawatan pesakit *"differentiated thyroid carcinoma"*

Tujuan: Untuk mengkaji penambahan nilai klinikal oleh SPECT/CT leher dan pengaruh ke atas rawatan pesakit *"differentiated thyroid carcinoma"*.

Metodologi: Skan radioiodin I-131 seluruh badan secara planar dan SPECT/CT leher dijalankan ke atas 78 pesakit yang telah disahkan secara histopatologi mengidap *"differentiated thyroid carcinoma"*. Hasil skan seluruh badan secara planar dan SPECT/CT leher telah dianalisis. Analisa klinikal berdasarkan klasifikasi TNM untuk tahap kanser, status kumpulan stratifikasi risiko terjadinya kanser berulang dan rancangan rawatan dibuat berdasarkan hasil skan seluruh badan secara planar dan SPECT/CT leher dan dibuat perbandingan. Seterusnya, analisa ini digunakan untuk menilai kesan atau impak terhadap perancangan rawatan pesakit secara keseluruhan.

Keputusan: Data daripada 78 pesakit dengan sejumlah 91 fokus radioiodin di bahagian leher diperiksa dan dianalisis oleh kedua-dua skan seluruh badan secara planar dan SPECT/CT leher. Pada analisis per fokus radioiodin, skan seluruh badan secara planar menghasilkan maklumat diagnostik pada 76 fokus (83.5%) di mana 49 fokus diklasifikasikan sebagai sisa kelenjar tiroid manakala baki 27 fokus diklasifikasikan sebagai nodus limfa. SPECT/CT leher menghasilkan maklumat diagnostik yang lebih besar iaitu pada 88 fokus radioiodin (96.7%). SPECT/CT leher telah mengubah diagnosis yang dibuat oleh skan radioiodin I-131 seluruh badan secara planar pada 30 fokus (33%, $p < 0.001$). Pada analisis per pesakit, hasil skan radioiodin I-131 seluruh badan secara planar telah diubah pada 29 pesakit (37.2%, $p < 0.001$) dari 78 pesakit selepas menilai maklumat yang dihasilkan oleh SPECT/CT leher. Klasifikasi tahap penyakit kanser tiroid menurut klasifikasi TNM telah disemak semula setelah mendapat maklumat yang diperolehi dari hasil SPECT/CT leher pada 8 (10.2%) dari 78 pesakit manakala kumpulan stratifikasi risiko terjadinya kanser berulang juga telah disemak semula selepas menilai maklumat yang dihasilkan oleh SPECT/CT leher pada 15 (19.2%) dari 78 pesakit. Secara keseluruhannya, hasil SPECT/CT leher telah memberikan perubahan yang ketara ke atas perancangan rawatan pesakit *"differentiated thyroid carcinoma"* ($p < 0.001$).

Kesimpulan: SPECT/CT leher telah menunjukkan kesan perbezaan diagnostik yang ketara berbanding dengan skan radioiodin I-131 seluruh badan secara planar. SPECT/CT leher juga memberikan kesan yang ketara ke atas perancangan rawatan pesakit *"differentiated thyroid carcinoma"*.

Kata Kunci: Differentiated thyroid carcinoma, iodine-131, planar scintigraphy, SPECT/CT.

Abstract

The incremental value of I-131 SPECT/CT of the neck in the management of differentiated thyroid carcinoma.

Aim: To assess the clinical value of single-photon emission computed tomography/computed tomography (SPECT/CT) of the neck in the management of differentiated thyroid carcinoma (DTC).

Material and methods: I-131 planar whole body scan and SPECT/CT of the neck were performed in 78 patients with histologically confirmed diagnosis of differentiated thyroid carcinoma. The scan findings made by each I-131 planar whole body scan and SPECT/CT of the neck were analysed. Clinical staging based on TNM staging classification and risk stratification group were assessed and compared based on information given by each I-131 planar whole body scan and SPECT/CT of the neck. Subsequently, clinical management plan made by each planar and SPECT/CT of the neck were assessed and compared for significant impact on overall patient management.

Results: Data from 78 patients with total of 91 radioiodine foci in the neck region was observed and analysed by both I-131 planar whole body scan and SPECT/CT of the neck. On lesion based analysis, I-131 planar whole body scan yield diagnostic information in 76 foci (83.5%) in which 49 foci were classified as thyroid remnant while the remaining 27 foci were classified as lymph node. SPECT/CT of the neck yield a better diagnostic information in 88 foci (96.7%). SPECT/CT of the neck has changed diagnosis given by I-131 planar whole body scan in 30 foci (33%, $p<0.001$). On patient based analysis, the findings of I-131 planar whole body scan were altered in 29 (37.2%, $p<0.001$) out of 78 patients in based on SPECT/CT findings. Clinical staging according to TNM classification was revised with additional information obtained by using SPECT/CT in 8 (10.2%) of 78 patients. The risk stratification group was revised with additional information obtained from SPECT/CT in 15 (19.2%) of 78 patients. SPECT/CT of the neck may significantly alter the personalised treatment planning for each patient with differentiated thyroid carcinoma ($p<0.001$).

Conclusion: SPECT/CT of the neck has shown a significant diagnostic impact as compared to I-131 planar whole body scan alone. SPECT/CT also had a significant impact on the management of patients with differentiated thyroid carcinoma.

Keyword: Differentiated thyroid carcinoma, iodine-131, planar scintigraphy, SPECT/CT.

CHAPTER 1

RESEARCH BACKGROUND

1.1 Introduction

Differentiated thyroid carcinoma (DTC) arising from thyroid follicular epithelial cells is a slow-growing malignancy which accounts for the vast majority (90%) of all thyroid cancers. Histologically, DTC consists of two subtypes, namely papillary carcinoma which comprises the large group (85%) of DTC and follicular carcinoma (10%) while the remaining (5%) of the DTC cases are from these two cells variant (Omar *et al.*, 2006).

According to *Malaysian National Cancer Registry Report for the period of 2007-2011* (2012), thyroid cancer was ranked seventeenth among males and ninth among females. Based on gender, there is female preponderance for DTC with female to male ratio is approximately 3:1 and the lifetime risk for thyroid cancer was 1 in 336 for females and 1 in 884 for males. Staging was reported for 671 cases in females and 213 cases in males, 60% were diagnosed at stage I and II in females and 48% in males. The incidence rate based on ethnicity was the highest among Malays (72.5%), followed by Chinese (22.6%), Indian (6.6%) and others (12.1%).

The prognosis of DTC is highly favourable. The United State National Cancer Database for Thyroid Carcinoma has reported that patient with papillary and follicular thyroid carcinoma has a high 10-year overall survival rate of 93% and 85%, respectively (Enewold *et al.*, 2009). Another study has reported that the 10-year overall survival rate was 76.8% while cause-specific survival rates was 84.9% (Eustatia *et al.*, 2006). As in the case of other malignant tumours, the mortality of this disease depends on several factors. Disease prognosis is critically determined by the presence of regional or distant metastases. A study has concluded that in thyroid carcinoma the overall survival and diseases recurrence are significantly influenced by involvement of regional lymph node metastases (Scheumann *et al.,* 1994). Moreover, lymph node metastases remained as an independent highly significant prognostic marker for more aggressive DTC regardless of the other risk factors such as older age, tumour invasion and distant metastases (Podnos *et al.*, 2005; Durante *et al.*, 2006). This evidence was also supported in a study which reported that in patients with metastasis, the 10-year overall survival rates has significantly decreased to 24% and cause-specific survival rate has also decreased to 27%, significantly (Dinneen *et al.*, 1995).

Despite the favourable prognosis, optimal outcomes are achieved only via coordinated multiple treatment modality. The goal of initial therapy of DTC are to remove the primary malignant tumour and locoregional involvement therefore to minimize risk of disease recurrence and also regional and distant metastatic disease. These can be achieved with the worldwide accepted initial treatment which consist of surgical removal of thyroid glands (total thyroidectomy) followed by radioiodine ablation therapy (RAI) with Iodine-131 (Luster *et al.*, 2008; ATA Guidelines, 2009;).

1.2 Literature Review

Radioiodine ablation therapy has been established as an effective adjuvant therapy for patients with DTC. It utilizes Iodine-131 as theranostic radioisotope which emits gamma rays for scintigraphic imaging for diagnostic purpose and beta particles for therapeutic effect (DeGroot *et al.*, 1990; Samaan *et al.*, 1992; Mazzaferri *et al.*, 1994).

Iodine-131 is concentrated within tissues expressing sodium iodide symporters (NIS) including thyroid cells and metastatic DTC. NIS expression is the determinant factor for selective Iodine-131 uptake in both normal thyroid tissues and in up to 80% of thyroid carcinoma cells. This uptake occurs through an electrochemical sodium gradient generated by sodium-potassium adenosine triphosphates. Therefore, this important tumour cell characteristic makes Iodine-131 a useful therapeutic as well as diagnostic (theranostic) tool for the management of DTC (Oh *et al.*, 2012).

NIS is physiologically expressed in various glandular cells: thyroid cells, ductal cells of salivary glands, parietal and mucous-secreting cells lining of the gastric mucosa, lacrimal glands, choroid plexus, ciliary bodies of the eye, thymus, placenta, and lactating mammary glands. NIS expression is also detected in most neoplastic cells of locoregional and distant metastases of DTC. As a consequence, Iodine-131 whole body scan (WBS) may show radioiodine uptake not only in thyroid remnants or metastases from DTC, but also in physiological non-thyroidal NIS expression tissue (Oh *et al.*, 2012).

Previous studies have found that radioiodine therapy improves the clinical prognosis of patients provided there is accumulation of Iodine-131 in the metastatic foci, despite having distant metastases. These iodine-131 avid metastatic foci have shown histological characteristic of DTC (Schlumberger *et al.*, 1996; Bernier *et al.*, 2001). Therefore, an accurate and precise localization and structural characteristic of iodine-131 avid metastatic foci are essential in the diagnosis of local recurrence, lymph nodes metastases and distant metastatic sites. Hence, the reliable and accurate determination of cancer staging based on TNM classification and risk stratification group for cancer recurrence and eventually, the adequate clinical follow-up and management of patients with differentiated thyroid carcinoma. Correctly interpreted findings of Iodine-131 scintigraphy can be of great benefit for patients with DTC.

Conventionally, the Iodine-131 scintigraphy has been performed as a whole-body planar scan (WBS). This planar scintigraphy in association with routine biochemical marker measurements (serum thyroglobulin, serum anti-thyroglobulin-antibody and serum TSH) are still considered as part of the routine diagnostic procedure for DTC patients in Malaysia. This modality is used in the detection of remnant thyroid tissue and locoregional or distant metastases after total thyroidectomy for initial staging and after radioiodine ablation therapy for restaging and long-term follow-up. However, the image may be noisy and have low resolution because it is a projection image from a higher-energy radioisotope, Iodine-131. Furthermore, the lack of anatomical landmarks as well as the possibility of various other benign or physiological Iodine-131 uptake, may complicate the image interpretations (Xue YL *et al.*, 2013). In the era of emerging advanced medical imaging system, single photon emission computed tomography/computed tomography (SPECT/CT) has been increasingly used. Diagnostic accuracy of SPECT has been reported to be improved by new SPECT/CT fusion images in various clinical situations (Kohlfuerst *et al.*, 2009). Therefore, their timely recognition may lead to accurate detection of an otherwise clinically occult tumour at an early and highly treatable stage.

Iodine-131 SPECT/CT has been demonstrated to overcome the limitation or pitfall of planar imaging by accurate and precise localisation and characteristic of pathological and physiological sites of radioiodine uptake. A study done among 123 patients with DTC in 2010 have shown that the sensitivities of SPECT/CT and planar imaging were comparable and did not show superiority in one to another (both 62%) (Menges *et al.*, 2012). However, specificity of planar imaging has significantly improved by SPECT/CT with specificity of 78% and 98%, respectively (Thust *et al.*, 2009). Another study to assess the diagnostic performance of co-registered SPECT/CT compared to Iodine-123 planar WBS imaging and to SPECT alone in patients with DTC has showed that there is no significant difference in sensitivity of planar WBS (41%) as compared to SPECT (45%) and SPECT/CT (50%) imaging. However, the specificity of planar WBS (68%) has significantly improved by the addition of SPECT (89%) and SPECT/CT (100%) imaging. Moreover, SPECT/CT was also showed a significantly higher positive predictive value (PPV 100%) as compared to planar WBS (31%) and SPECT alone (59%) (Barwick *et al.*, 2009). This data has proven that the diagnostic information has significantly improved by addition of SPECT/CT as compared to planar WBS or SPECT imaging alone (Tharp *et al.*, 2004). The clinical value of SPECT/CT in the management of DTC patients is still being investigated by many authors. Previous studies so far had shown diverse results because of various target populations, different clinical settings and different analysis protocols (Tharp *et al.*, 2004; Ruf J. *et al.*, 2004; Chen *et al., 2008;* Wong *et al.*, 2008; Schmidt *et al.*, 2009; Kohlfuerst *et al.*, 2009; Grewal *et al.*, 2010; Wong *et al.*, 2010; Yasuhiro M *et al.,* 2012; Menges *et al.,*2012; Valentina *et al.,* 2016).

1.3 Research Problem

In the era of emerging advanced imaging modality, without any doubt studies has proven that SPECT/CT has superior diagnostic accuracy as compared to conventional planar scintigraphy in various clinical situations. In the case of DTC, SPECT/CT have been reported to improve the diagnostic accuracy in detecting nodal and distant metastases as compared to planar scintigraphy alone. Iodine-131 SPECT/CT has also been demonstrated to overcome the limitation or pitfall of planar scintigraphy in characterizing and localizing pathological and physiological sites of radioiodine uptake.

SPECT/CT has been introduced to our institution since early 2014. Ever since, SPECT/CT in addition to planar scintigraphy has shown a significant impact to our service of care in various aspect. SPECT/CT has increased the level of confidence among nuclear medicine doctors in interpreting various type of nuclear medicine scintigraphy including the radioiodine scintigraphy performed for all patients treated with radioiodine ablation therapy. Nevertheless, the clinical value of SPECT/CT in the management of differentiated thyroid carcinoma patients in Malaysian populations is yet to be investigated.

Despite the facts, SPECT/CT hybrid imaging is quite a new modality with limited availability in the government hospitals in Malaysia. As a consequence, Iodine-131 planar scintigraphy has remained the standard procedure for patient with DTC who undergoes radioiodine ablation therapy in Malaysia.

The question arises whether the additional value of SPECT/CT hybrid imaging may provide a clinical relevance to the management of patient with DTC and eventually give a significant impact to the standard quality of care in Malaysia?

1.4 Justification of Study

We conduct a study which aim to provide evidence of the incremental value and clinical relevance of SPECT/CT of the neck in the management of patient with DTC who had radioiodine ablation therapy and therefore improving the standard quality of care in Malaysia.

1.5 Objectives

1.5.1 General Objective

- To assess the clinical value of SPECT/CT of the neck in the management of DTC.

1.5.2 Specific Objectives

- To determine the correlation of image interpretation between planar WBS and SPECT/CT of the neck.
- To determine the significance of SPECT/CT diagnostic value on staging and risk stratification of DTC.
- To determine the impact of SPECT/CT diagnostic value on therapeutic planning for DTC.

1.6 Research Hypothesis

Null Hypothesis

- SPECT/CT of the neck has no significant incremental clinical value in the management of patient with DTC.

Alternate Hypothesis

- SPECT/CT of the neck has significant incremental clinical value in the management of patient with DTC.

CHAPTER 2

MATERIALS AND METHODS

2.1 Study Design and Location

This prospective cohort study was conducted in Nuclear Medicine Department, Kuala Lumpur General Hospital.

2.2 Study Population and Recruitment Time Frame

The study population was derived from patients with histopathologically confirmed diagnosis of DTC and had undergone total thyroidectomy. They were referred to Nuclear Medicine Department, Hospital Kuala Lumpur for radioiodine ablation therapy. The post therapy scintigraphy (RxWBS) showed radioiodine sensitive foci in the neck with no other abnormal distant foci elsewhere. They are recruited into this study when the subsequent scheduled diagnostic scintigraphy (DxWBS) showed persistent positive foci in the neck.

The data collection duration was between 1st April 2016 till 30th April 2017.

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion criteria

1. Male/female aged ≥ 18 years' old
2. Histopathologically confirmed diagnosis of DTC
3. Had total thyroidectomy
4. Undergo radioiodine ablation therapy
5. Had persistent radioiodine sensitive foci in the neck with no other abnormal distant foci elsewhere in both post therapy scintigraphy (RxWBS) and subsequent diagnostic scintigraphy (DxWBS).

2.3.2 Exclusion criteria

Patient who does not give consent to this study.

2.4 Ethical board

The study was approved by the Universiti Sains Malaysia Human Research Ethics Committee and Medical Research and Ethics Committee, Kementerian Kesihatan Malaysia (refer appendix 4 (a) and (b)). Written informed consent was obtained from all the patients who were included in the study.

2.5 Sample Size Calculation

The sampling population was derived from DTC patients who were referred to Nuclear Medicine Department, Hospital Kuala Lumpur for radioiodine ablation therapy. Total new DTC patient per annum was 97 patients in 2015 (based on source from Nuclear Medicine Department, Hospital Kuala Lumpur patient data registry). The prevalence of regional lymph node metastasis (neck region) in DTC patient is 20-50% (ATA Guidelines, 2009).

The sample size calculation was done using Epi Info 3.1.5 based on sample size formula for population survey. The required sample size to achieve a power of 80% and confidence interval of 95% is 70 patients.

2.6 Research Tool

a. Data sheet to compile patient's information (refer appendix 1).
b. Data sheet for data collection for each patient (refer appendix 2a).
c. Data sheet for follow-up data (refer appendix 2b)

2.7 Sampling Method and Procedures

The following procedures had been carried out during the patient recruitment:

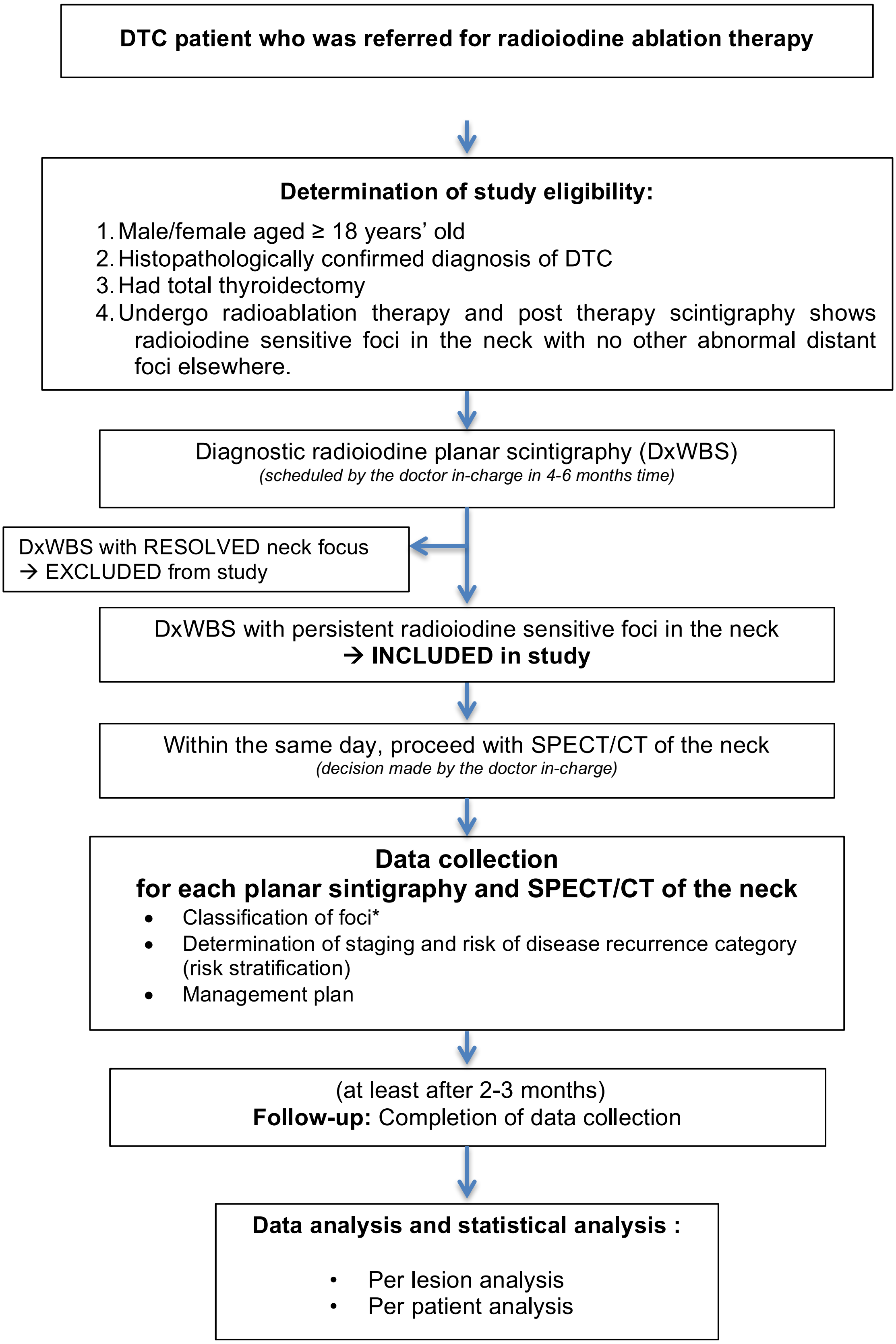
1. All DTC cases referred to Nuclear Medicine Department, HKL for radioiodine ablation therapy had been discussed during clinical meeting with Nuclear Medicine Specialist and then scheduled for radioiodine ablation therapy.
2. Following the radioiodine ablation therapy, patient was routinely undergone post therapy scintigraphy (RxWBS).
3. All patients with RxWBS result of radioiodine sensitive foci in the neck (with no other abnormal distant foci elsewhere) were identified. The doctor in-charge scheduled them for next diagnostic iodine-131 scintigraphy (DxWBS) in 4-6 months' time.
4. On the appointment day for DxWBS, the doctor in-charge clerked and performed physical examination to the patient. After taking low dose radioiodine, patient was discharged and came back in 2-3 days time for DxWBS.
5. On the DxWBS scan day, all patients with resolved radioiodine sensitive foci in the neck were excluded from this study.
6. The patients with persistent radioiodine sensitive foci in the neck were included into this study. The patients then proceeded with SPECT/CT of the neck on the same day.

7. Both planar and SPECT/CT findings were interpreted by the Nuclear Medicine Specialist in-charge and further management plan decided was documented in the patient's folder.
8. The patient was given an appointment date for clinic follow-up in at least two to three months' time by the doctor in-charge to review any investigation results to support the diagnosis including the histopathological report or other imaging modalities (US, diagnostic CT or MR) report and the results of relevant biochemical markers.
9. The patient had been explained about the study details beforehand. Informed consent had been signed for their participation in this study.
10. Data collection was recorded in data collection forms (refer appendix 1 and 2) for further data analysis.

The procedures mentioned above was a standard procedure for the management of DTC patient referred to Nuclear Medicine Department, HKL for radioiodine therapy. A written informed consent was obtained for the participation of the patient in this study and data collection.

Patient's management plan was made by the Nuclear Medicine Specialist in-charge regardless their participation in the study. Data collection for the study purpose were the secondary data obtained from the patient's file and scan reports including whichever result available during the follow-up as reference standard.

2.8 Conceptional Framework (Flow Chart)



*Classification of radioiodine sensitive foci (Schmidt *et al.*, 2009):

1. Thyroid remnant [focus +]
2. Radioiodine sensitive lymph node [focus +]
3. Indeterminate focus (Equivocal)
4. Benign/physiological focus [focus -]

**Reference Standard (Chen *et al.,* 2008; Yasuhiro M *et al.,* 2012).

The reference standard is to confirm the diagnosis of the radiosensitive foci from the interpretation of the iodine-131 scintigraphy alone or with SPECT/CT images. The reference standard is at least one of the following methods:

a. Histopathological diagnosis of tissue sample taken from surgical resection or tissue biopsy.
b. Diagnostic imaging of the neck by using other diagnostic imaging modalities i.e. US, diagnostic CT or MR imaging.
c. Clinical follow-up with biochemical data (serum thyroglobulin, serum anti-thyroglobulin-antibody, serum TSH) at least after two to three months.

2.9 Variable Definitions

a. Planar whole body scan (Schmidt *et al.*, 2009).

Radioiodine sensitive focus is defined as any focus with uptake greater than the background level; is localised according to reader observation:

- Benign/Physiological focus: uptake in the nose and symmetrical uptake in the salivary glands
- Thyroid remnant:
    - Focus of uptake localized in the thyroid bed or
    - Midline focus superior to the thyroid bed (pyramidal lobe)
- Radioiodine sensitive lymph node: Focus at a greater distance lateral to the thyroid bed
- Indeterminate focus (Equivocal):
    - Focus adjacent to the thyroid bed or medial portion of the neck
    - Asymmetrical focus within the level of the neck

<u>b. SPECT/CT of the neck (Schmidt *et al.*, 2009).</u>

SPECT/CT of the neck: The field of view covers from basal of skull to the level of mid sternum.

Radioiodine sensitive focus is defined as all foci with uptake greater than the background level with CT correlation of specific anatomical structure:

- Benign/Physiological: Physiologic anatomical structure.
- Thyroid remnant: Focus of uptake localized in the thyroid bed/pyramidal lobe.
- Radioiodine sensitive lymph node: Focus in levels I–VI and VII collocated with lymph node visible on CT (The localisation of the node is according to the cervical lymph node classification levels published by the 7th AJCC in 2009)
- Indeterminate focus (Equivocal): Focus in levels I–VI and VII without lymph node visible on CT.

2.10 Data and Statistical Analysis

2.10.1 Data Collection tool and data management.

A data collection forms (appendix 1 and 2) were designed for the purpose of data collection. Appendix 1 is the form consist of patients' demographic information, clinical features and the other relevant investigation results and treatment history. Appendix 2 is divided into section A and B. Section A covers the result of I-131 planar scintigraphy and SPECT-CT image interpretations and analysis. Section B covers the supportive data from any of the reference standards. The source of data are from the patients' medical record and the scintigraphic images.

Data has been keyed-in into spreadsheet MS excel which was then exported to STATA version 11 (1) to proceed with data cleaning and data analysis.

2.10.2 Statistical analysis

A generalized McNemar or Stuart–Maxwell test was used to determine whether the assignment of scan findings, TNM staging, risk stratification and management plan by planar WBS and SPECT/CT of the neck had the same distribution. In addition, a weighted kappa statistic was computed to estimate the level of concordance/agreement between the two methods, with regard to TNM staging and risk stratification. Table 1 shows the guidelines for interpreting kappa statistics as suggested by Landis and Koch

Table 1: Interpretation of kappa statistic

Kappa	Agreement
<0	poor agreement
0.01–0.20	slight agreement
0.21–0.40	fair agreement
0.41–0.60	moderate agreement
0.61–0.80	substantial agreement
0.81–1.00	almost perfect agreement

The findings of planar WBS and SPECT/CT of the neck were compared with the reference standard of either a histopathologic diagnosis, diagnostic imaging by using other modalities of US, diagnostic CT or MR imaging or clinical follow-up with biochemical data (serum thyroglobulin, serum anti-thyroglobulin-antibody and serum TSH). For the purpose of these calculations, equivocal findings were excluded by each method. Comparison of the diagnosis of DTC by each method was performed using an exact McNemar's test.

All p-values reported were two sided, and a p-value of less than 0.05 was taken as the critical limit to determine the significance difference. Data were analysed using Stata software (Stata/SE 14, College Station, TX, USA).

2.11 Privacy and Confidentiality

In order to protect the patients' privacy and confidentiality, management of confidential information of the research subject is crucial. To meet the purpose, each of the participants subjected into the study has been given specific code number to create a 'clean' data set. This clean data set did not contain information the subject's identification. The identifying information including the master reference list of patients with the code number and other document containing subject information has been kept safely according to the following data protection plan:

1. All files containing data in the computer has been kept with password protection.
2. All removable storage media holding the data (e.g., CDs, hard disk, removable drive, etc.) are kept in a locked compartment when not in use
3. Printouts derived from data analysis stored in a locked compartment when not in use.

All these documents will be kept in storage for 5 years and then will be destroyed in a secure manner.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Results

3.1.1 Patient Demographics

A total number of 78 patients with histologically confirmed differentiated thyroid carcinoma were identified and included in the study. The demographic details of the patients are shown in table 2. I-131 planar WBS and immediately followed by SPECT/CT of the neck were done for all the patients. From the total number of patients, 58 (74.4%) were females and 20 (25.6%) patients were males.

The patients were predominantly Malays which comprised of slightly more than half of the total cases at 64.1%, followed by Chinese 19.2%, Indian 11.5% and others 5.1%.

The mean age at diagnosis is 42 years old. For the purpose of TNM staging for thyroid carcinoma, the patients were divided into two age groups; age group of less than 45 years old which comprised of 40 patients (51.3%) and age group of equal or more than 45 years old which comprised of 38 patients (48.7%) from the total number of patients included in the study.

Majority of the patients were diagnosed with papillary thyroid carcinoma which comprised of 85.9%, followed by follicular thyroid carcinoma which comprised of 11.5%. Other type of thyroid carcinoma (ie. Hurtle Cell Carcinoma) was identified in two patients which comprised of 2.6%.

Table 2: The demographic profiles of the study population (N=78)

	n	**(%)**
Age at diagnosis, years*:		
Mean (SD)	42.73 (16.46)	
Range	18, 74	
Gender:		
Male	20	(25.6)
Female	58	(74.4)
Race:		
Malay	50	(64.1)
Chinese	15	(19.2)
Indian	9	(11.5)
Others	4	(5.1)

**Numerical values.*

SD = Standard deviation; Range = minimum, maximum.

Figure 1: Bar chart shows the distribution of study population by age group (N=78)

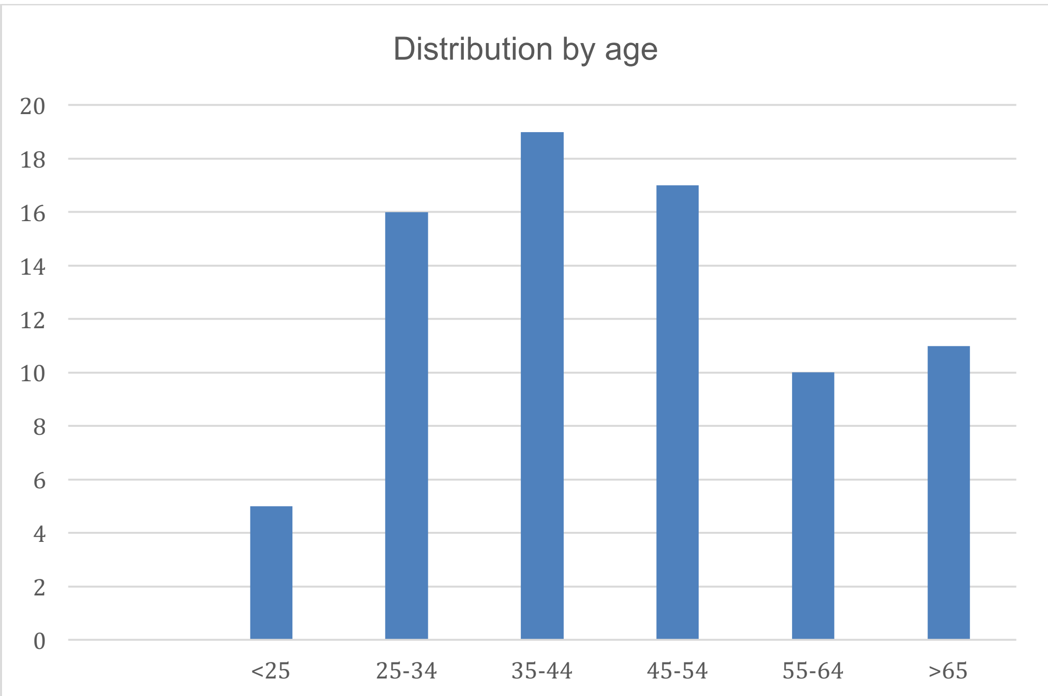


Figure 2: Pie chart shows the distribution of study population by ethnicity/race (N=78)

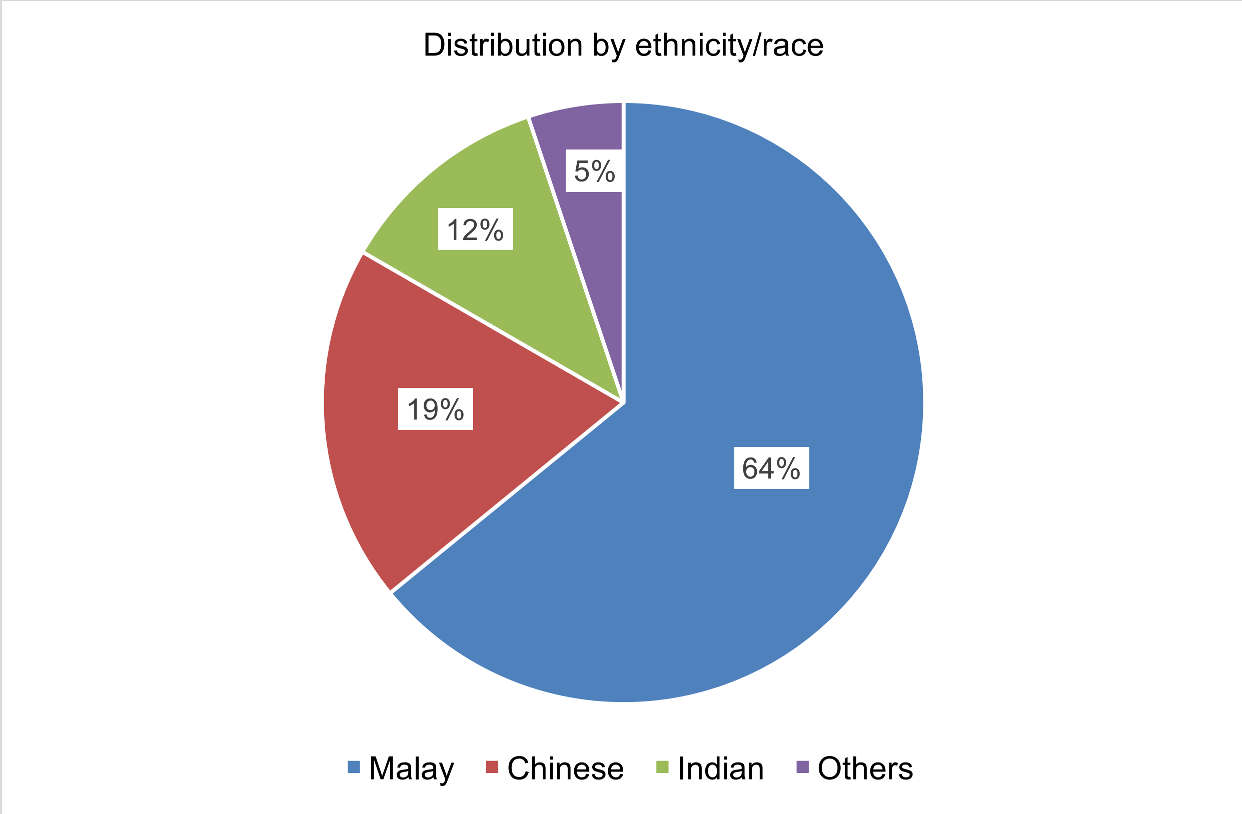
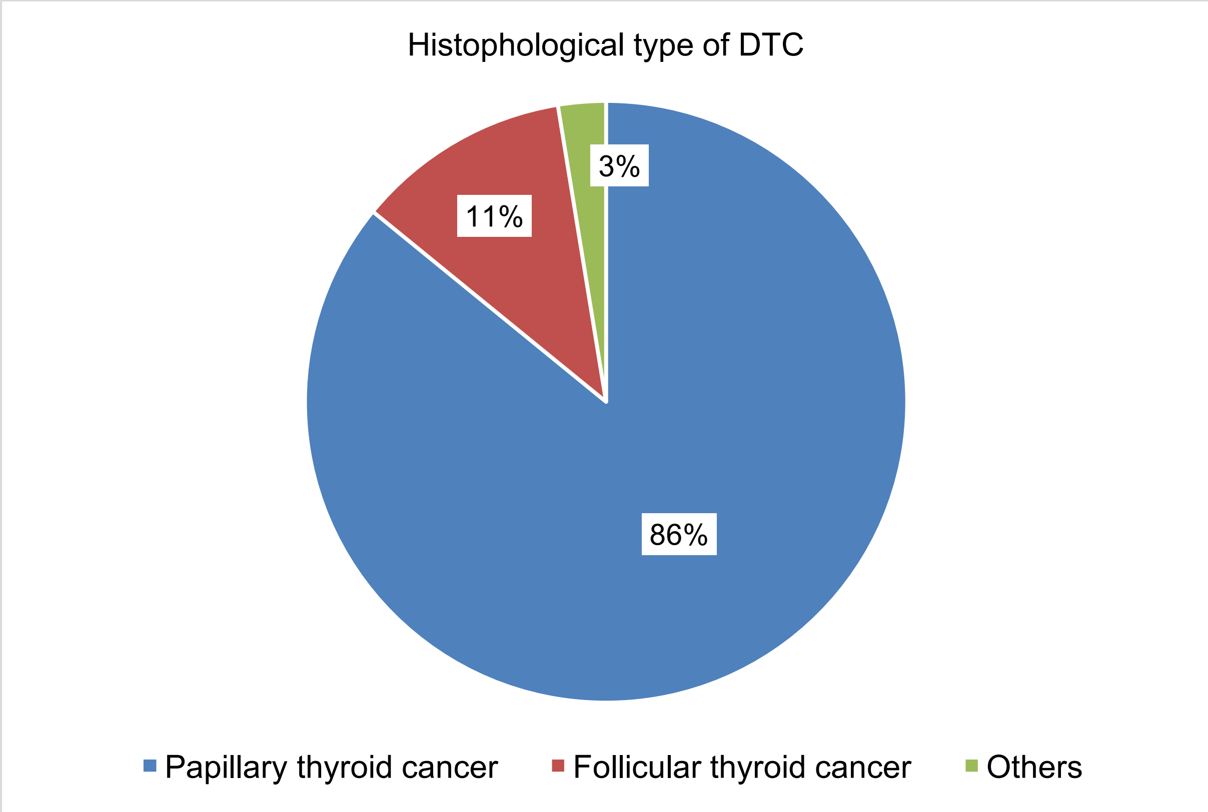


Table 3: The histopathological type of the study population (N=78)

	n	**(%)**
Histopathological type:		
Papillary thyroid cancer	67	(85.9)
Follicular thyroid cancer	9	(11.5)
Others	2	(2.6)

**Numerical values.*

Figure 3: Pie chart shows the histopathological type of the study population (N=78)



3.1.2 Lesion Based Analysis

In 78 patients, there were 91 foci observed on both I-131 planar WBS and SPECT/CT of the neck. The SPECT/CT of the neck were done on all the 78 patients which I-131 planar WBS showed uptake greater than the background level. I-131 planar WBS yield diagnostic information in 76 foci (83.5%) in which 49 foci were classified as thyroid remnant while the remaining 27 foci were classified as lymph node. SPECT/CT of the neck yield a better diagnostic information in 88 foci (96.7%). 38 foci were classified as thyroid remnant, 33 foci as lymph node and the remaining 17 foci were classified as benign or physiological foci.