DIFFERENTIATED THYROID CANCER: CHANGES IN THE PULMONARY FUNCTION TEST POST FIRST RADIOACTIVE IODINE TREATMENT

by

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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 in Nuclear Medicine. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as reference.

Sincerely,

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ABBREVIATIONS

AJCC	American Joint Committee against Cancer
ATA	American Thyroid Association
DLCO	Diffusing capacity of the lungs for carbon monoxide
DTC	Differentiated Thyroid Cancer
ETE	Extrathyroidal Extension
FEV1	Forced expiratory volume in 1 second
FNAC	Fine Needle Aspiration Cytology
FTC	Follicular Thyroid Cancer
FVC	Forced vital capacity
HUSM	Hospital Universiti Sains Malaysia
ICRP	International Commission on Radiological Protection
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
mCi	milliCurie
mPTC	Papillary Microcarcinoma
MOH	Ministry of Health
PFT	Pulmonary Function Test
PI	principal investigator
PTC	Papillary Thyroid Cancer
RAI	Radioactive iodine
RLF	Radiation lung fibrosis
T4	Thyroxine
Tg	Thyroglobulin
TNM	Tumor, lymph node and metastasis
TSH	Thyroid Stimulating Hormone
UICC	Union for International Cancer Control
WBS	Whole body scan

ABSTRAK

Pendahuluan: Kanser tiroid jenis diferensiasi atau dibezakan: Perubahan pada keputusan pemeriksaan fungsi peparu selepas menerima rawatan pertama radioaktif iodin.

Pengenalan: Penyakit tiroid boleh dibahagikan kepada jenis yang merbahaya seperti kanser dan juga tidak merbahaya. Rawatan bagi penyakit tiroid telah lama dipraktikkan berdasarkan garis panduan yang dikeluarkan oleh Persatuan Tiroid Amerika. Radioaktif iodin atau Iodin-131 digunakan sebagai rawatan untuk kanser tiroid dan penyakit hipertiroidisma(kadar hormon tiroid yang tinggi). Keradangan peparu dan fibrosis peparu ialah antara komplikasi yang dialami oleh pesakit yang menerima rawatan iodin-131. Pesakit kanser tiroid jenis dibezakan mempunyai jangka hayat yang lebih lama berbanding pesakit kanser yang lain walaupun kanser telah merebak jauh ke organ lain. Oleh itu, peparu yang berfungsi dengan baik adalah penting untuk kelangsungan hidup dan kualiti hidup. Kajian terbaru ke atas pesakit yang mempunyai kanser tiroid yang merebak ke peparu mendapati bahawa fungsi peparu berkurangan semasa lawatan susulan.

Objektif: Tujuan penyelidikan adalah untuk menilai perubahan fungsi peparu dalam pesakit kanser tiroid selepas terdedah kepada rawatan iodin-131 yang pertama dan untuk mencari perbezaan fungsi peparu antara pesakit dengan atau tanpa merebak ke peparu.

Kaedah: Pesakit kanser tiroid yang telah melakukan pembedahan pembuangan tiroid dan dirujuk untuk rawatan iodin-131 dinilai dan diambil sebagai peserta kajian. Pesakit ini melakukan pemeriksaan fungsi peparu yang pertama iaitu sebelum memulakan rawatan

iodin-131. Pemeriksaan fungsi peparu yang kedua dan ketiga dilakukan 3 dan 6 bulan selepas rawatan diberikan. Data klinikal dianalisa menggunakan perisian IBM SPSS.

Keputusan: Seramai 49 peserta dengan median dan min berumur lingkungan 40 tahun telah terlibat dan kebanyakannya terdiri daripada wanita (88%). 65% terdiri daripada kaum Melayu. Lapan pesakit menghidapi kanser yang telah merebak ke peparu. 2 daripadanya dikesan melalui skan pengimejan tomografi berkomputer sebelum menerima rawatan iodin-131, manakala selebihnya melalui skan seluruh badan iodin-131. 24 peserta mempunyai bacaan awal fungsi peparu yang normal. Median bacaan asas fungsi peparu bagi kapasiti vital paksa (FVC)=79%, isipadu hembusan paksa dalam 1 saat (FEV1)=84% dan FEV1/FVC=88. Tiada perubahan yang signifikan bagi bacaan FVC, FEV1 dan FEV1/FVC, 3 dan 6 bulan selepas rawatan iodin-131 ($p=0.985$, $p=1.0$ dan $p=0.58$ masing-masing). Tiada perubahan fungsi peparu yang signifikan juga bagi pesakit yang mempunyai bacaan asas yang normal atau tidak normal dan juga untuk pesakit yang merebak ke peparu atau tidak.

Kesimpulan: Tiada kemerosotan pada fungsi peparu yang signifikan selepas menerima rawatan pertama iodin -131 walaupun di kalangan pesakit bacaan asas yang tidak normal atau pesakit kanser yang merebak ke peparu

Perkataan Utama: Kanser tiroid, Perubatan Nuklear, Pengimejan Radionuklid, Rawatan Iodin-131, Ujian Fungsi Peparu

ABSTRACT

Title: Differentiated Thyroid Cancer: Changes in The Pulmonary Function Test Post First Radioactive Iodine Treatment

Introduction: A thyroid disease could be benign or malignant. Management of thyroid disease has been well established and documented following the American Thyroid Association Guidelines. Radioactive Iodine (RAI) or Iodine-131 (^{131}I) is used to treat differentiated thyroid cancer and benign hyperthyroidism. Radiation pneumonitis and lung fibrosis are lungs complication beside other complication after the exposure of Iodine-131. Differentiated Thyroid Cancer (DTC) patients have longer survival rate as compared to other solid tumour even if the patients had distant metastasis at first diagnosis. Thus, having good lung function is essential for the survival and quality of life. Recent study showed that lung function of some patients with lung metastasis has been found severely impaired during follow-ups.

Objective: The aim is to evaluate changes of pulmonary function in DTC patients after exposure to first Iodine-131 treatment and to look for differences between patients with or without lung metastasis

Methods: Post total or near total thyroidectomy differentiated thyroid cancer patients referred for first Iodine-131 treatment were evaluated and recruited as study subjects. These patients had the pulmonary function test (PFT) before the first Iodine-131 treatment started.

Repeated PFT was performed at 3 and 6 months after the first Iodine-131 treatment. Clinical data was analysed using IBMM SPSS software.

Results: A total of 49 patients with the median and mean age of 40's were recruited and the majority were females (88%) and by ethnicity, the majority were Malay which was about 65%. 8 patients had metastasis whereby 2 were diagnosed based on computed tomography (CT) findings during pre- Iodine-131 ablation and the rest based on post Iodine-131 treatment whole body scan. 24 patients had normal baseline PFT. The median value of baseline PFT was forced vital capacity (FVC)=79%, forced expiratory volume in 1 second (FEV1)=84% and FEV1/FVC=88. There were no significant changes of FVC, FEV1 and FEV1/FVC after 3 and 6 months of Iodine-131 ablation ($p=0.985$, $p=1.0$ and $p=0.58$ respectively). There were also no significant changes of PFT for patients with normal or abnormal baseline as well as for patients with or without lung metastasis.

Conclusion: There was no significant worsening of pulmonary function test in the differentiated thyroid cancer patients after their first radioactive iodine treatment even for patients with abnormal baseline or patients with lung metastasis.

Keyword: Thyroid cancer, Nuclear Medicine, Radionuclide imaging, Radioactive Iodine Therapy, Pulmonary function test

1.0 INTRODUCTION & LITERATURE REVIEW

1.1 Thyroid Cancer

1.1.1 Definition and Demographics

Thyroid cancer is known as the most common malignancy of endocrine but it only accounts for 1% of malignancy of all tumours. The incidence of thyroid cancer is on the rise over the years due to public awareness and advancement of imaging modalities on detecting thyroid cancer including microcarcinoma of the thyroid. Microcarcinoma is referring to a tumour, which is of less than 1cm in longest diameter (Ziessman *et al*, Haugen *et al*). There were 2 million patients globally diagnosed with thyroid cancer in 2015 (Murtaza Mustafa, 2017).

The incidence of thyroid cancer was higher in goitre prevalence community, a benign condition of thyroid disease. Locally, 7 states in Malaysia have been identified by MOH as an endemic area of goitre. Thyroid cancer was listed in top 5 cancers in the endemic states of goitre like Sabah and Kelantan, while it was not even listed in top 10 cancers in Penang, as it was a non-endemic state of goitre. (Othman N.H. *et al*, 2018). Another study done by Othman N.H. *et al* (2009) in Kelantan from year 1994 to 2004, about 60% of thyroid cancer patients also have background of prolonged goitre.

According to the latest local data from the MALAYSIAN NATIONAL CANCER REGISTRY REPORT 2007 – 2011, by National Cancer Institute, there were 103,507 new cancer cases reported in Malaysia. Thyroid cancer was the 9th commonest cancer among Malaysian women since 2007 until 2011, which was about 3% of all types. In the age group of 15-24 years old for both genders, thyroid cancer was the 4th commonest, which was about 10.7%. The highest incidence rate within ethnicity was Malays in both males and

females. Among Malay women, thyroid cancer ranked 8th, about 4.2% and among women of other ethnic groups, it ranked 10th which was 3.7% of all cancer. However, thyroid cancer was less common among Malaysian males generally and it was ranked 17th. In summary, the risk of thyroid cancer was 1 in 336 for women and 1 in 284 among Malay women while it was 1 in 884 for men and 1 in 734 among Malay men. 48% of male patients and 60% of female patients were diagnosed with stage I and II (Azizah Ab M, 2015). From Malaysia Cancer Incidence in Peninsular Malaysia 2002 – 2005, the male to female ratio was approximately 1:3 and this was comparable to that of the US and Singapore (Lim G.C.C. *et al*, 2008).

Thyroid cancer arises from follicular C-cell but some rare cancer arises from other cells such as lymphoma, sarcoma and hemangiosarcoma. Types of cancer are based on histological features that are papillary, follicular, medullary and anaplastic (Elisei *et al*, 2013). Papillary and follicular thyroid cancer arise from thyroid follicular cells and are defined as differentiated thyroid cancer (DTC) (Ziessman *et al*, 2014). DTC maintains its normal features of follicular cells hence maintain the ability to take up iodine and produce thyroglobulin. In most cases, papillary thyroid cancer (PTC) is the commonest histology, which accounts for 80% of all thyroid cancer followed by follicular thyroid cancer (FTC), at 10%. The most diagnosed Thyroid Cancer is the small PTC with an indolent clinical course (M.J. Jeon, 2018). The DTC normal feature also results in having good response towards RAI treatment, which subsequently leads to excellent prognosis and high survival rate (F. Pacini *et al*, 2012).

1.1.2 **Clinical Presentation and Risk Factor**

Clinically, the most common presentation of thyroid cancer is asymptomatic thyroid nodule or mass that can be felt in the neck. The nodule can be either single or multiple which is usually fixed and firm in consistency. Some nodule could rapidly increase in size over weeks or months. Study done by Abdullah *et al* (2002) in Kuala Lumpur found that single nodule variation was the main mode of presentation which accounts about 70% of the total cases, followed by generalised thyroid enlargement (19%) and cervical lymph node enlargement alone (5.6%).

The differentiation between benign and tumour is very important for the patients as it will lead to different overall management methods altogether. Some patients have obstructive features like dysphagia, difficulty of breathing and persistent cough as well as changes of voice due to involvement of laryngeal nerve and vocal cord palsy (Elisei *et al*, 2013). In some rare cases, patient would present with distant metastatic symptoms like bone pain and lymph nodes enlargement. A study done by Sothy K. (1991) in Kelantan established that there were 20% of patients presented with obstructive symptoms, 19% with bone metastases and 12% had cervical lymph node. Usually patients are euthyroid but patient with large or metastatic disease may present with hyperthyroidism or hypothyroidism (Murtaza M. *et al*, 2017).

Majority of patients (93.5%) had multinodular goitre prior to cancer (Sothy K. *et al*, 1991). Genetic predisposing factor and environmental are thought to be the risk factor of thyroid cancer (Murtaza M. *et al*, 2017, Ziessman *et al* 2014). First-degree relatives of thyroid cancer patients have 5.4 fold-increased risk of getting it followed by 2.2 and 1.8 fold for second and third-degree relatives (Oakley *et al*, 2013). Direct or indirect exposure

to ionising radiation increased the risk from 15 to 53 fold of getting DTC (Hancock *et al*, 1995). Several thousands of thyroid cancer cases were diagnosed among those who had been exposed to Iodine-131 from the nuclear reactor accident in Wind scale, Britain, Chernobyl, Soviet Union and Fukushima, Japan (McNally *et al*, 2016). Hence a complete medical history is crucial. Physical examination is also equally important e.g. examination of the neck to look for thyroid or nodule's characteristic, lymph node's involvement, obstructive features and extent of the disease (Elisei *et al*, 2013). However, obesity is still debatable as a predisposing factor of thyroid cancer (Murtaza M. *et al*, 2017).

1.1.3 **Investigation**

Ultrasound is a commonly used imaging method to detect the presence and characteristic of thyroid nodule as well as status of the whole thyroid gland (Murtaza M. *et al*, 2017; Haugen *et al*, 2016). It helps in measuring the size, number and extension of the nodule. Patterns of high suspicion of the nodule on ultrasound are solid hypoechoic or partially cystic, irregular margin or calcified margin with small extrusive soft tissue, microcalcification, taller than wide and evidence of extrathyroidal extension (ETE). The estimated risk of malignancy is between 70 to 90% (American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodule and Differentiated Thyroid Cancer by Haugen B.R. *et al*, 2015).

Fine needle aspiration cytology (FNAC) is usually performed following the ultrasound finding. It is also best done under ultrasound guided to reduce the incidence of false negative result by locating the nodule. The cytology finding should be reported base

on the Bethesda System provided by 2007 National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference (Haugen B.R. *et al*, 2015).

1.1.4 **Staging**

Thyroid cancer stage follows the American Joint Committee against Cancer (AJCC)/Union for International Cancer Control (UICC) TNM system, which refers to the size or extent of the tumour histopathologically (T), any lymph node spread (N) and distant metastasis (M), as shown in Table 1.1. Staging is required for cancer registries and predicting disease mortality.

From 2nd until 7th edition of AJCC, the age of cut-off for staging is 45 years old. Multiple studies have been done and recommended that the age cut-off needed to be increased to 55 years or using multiple age categories to have better reflection of relationship between age and prognosis (Yoon Lee *et al,* 2017). A total of 9484 patients from 10 different international institutions were included in a study done by Nixon *et al* in 2016 to validate the 55 years old as a cut-off for risk stratification. They found that the 10-year disease-specific survival (DSS) for stage I-IV were 99.7%, 97.3%, 96.6% and 76.3%, respectively, when using 45 years as a cut-off age. While the 10-year DSS for stage I-IV were 99.5%, 94.7%, 94.1% and 67.6%, respectively, when using 55 years as a cut-off age. Change in the cut-off age lead to downstaging of 12% of patients and the downstaged group had a 10-year DSS of 97.6%. This prevents overstaging of patients with low risk disease as well as provides a more realistic estimate of prognosis for patients who remain as high risk.

Updated version of 8th AJCC system was announced in mid-2016 and was effective in January 2018. The age of cut-off for staging is increased from 45 to 55 years at diagnosis.

Table 1.1: AJCC/UICC TNM Staging for Differentiated Thyroid Cancer 8th Edition, published in Head and Neck Pathology, Volume 12, Issue 3, September 2018 by Springer.

Age	Stage	
Under 55	I	Any size of tumour, located in the thyroid with or without lymph nodes or tissue
	II	Any size of tumour with distant metastasis
55 and above	I	Tumour no larger than 4cm and confined to the thyroid
	II	- Tumour of any size with nearby lymph node involvement - Tumour that has grown into the strap muscles around the thyroid with or without lymph node involvement
	III	Tumour has grown extensively into nearby tissues: larynx, trachea, oesophagus or laryngeal nerve with or without lymph node
	IVA	Tumour has grown extensively back toward the spine or into nearby large vessels with or without lymph node
	IVB	Tumour of any size with or without lymph node and has distant metastasis: lungs, distant lymph node, internal organ, bones and etc

The ATA guideline further divides patients with DTC into high, intermediate and low risk categories depending on histopathological examination (HPE), lymph node involvement, distant metastasis, Serum thyroglobulin (Tg) and RAI whole body scan (WBS) findings (Table 1.2). Patient will be treated according to their risk.

Table 1.2: ATA 2009 Risk Stratification System with Proposed Modification

LOW RISK	Papillary thyroid cancer: a) No metastases: local or distant b) All macroscopic tumour has been resected c) No tumour invasion of loco-regional tissue or structures d) The tumour does not have aggressive histology e) If ^{131}I therapy is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment WBS. f) No vascular invasion g) Clinical N0 or ≤5 pathologic N1 micrometastases(<0.2cm) Intrathyroidal, encapsulated follicular variant of PTC Intrathyroidal, well differentiated FTC with capsular invasion and no or minimal (<4 foci) vascular invasion. Intrathyroidal, papillary microcarcinoma (mPTC), unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known)
INTERMEDIATE RISK	Microscopic invasion of tumour into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment WBS Aggressive histology (tall cell, hobnail variant, columnar cell carcinoma)

	PTC with vascular invasion Clinical N1 or >5 pathologic N1 (all involved lymph nodes <3cm) Multifocal mPTC with ETE and $BRAF^{V600E}$ mutated
HIGH RISK	Macroscopic invasion of tumour into the perithyroidal soft tissue (gross ETE) Incomplete tumour resection Distant metastases Postoperative serum Tg suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3cm FTC with extensive vascular invasion (>4 foci)

1.1.5 **Distant Metastasis**

Distant metastasis of thyroid cancer, which is uncommon in DTC patients, with a wide range of prevalence (4-23%) has been reported and often viewed as life threatening (Song H.J. *et al*, 2015). The majority of deaths among thyroid cancer patients were indeed of those patients with distant metastatic disease. Long-term survival rate also has a wide range from 13 to 100% due to heterogeneity in patients (Kim H *et al*, 2018). They have varying clinical outcomes from complete remission to rapidly progression and death (Song H.J. *et al*, 2015). In high risk patients especially those presented with extrathyroidal extension or massive nodal involvement, the distant metastasis can be evaluated with RAI post-surgery.

Lungs are the most common sites of distant metastasis. Diagnosis of lung metastases was based on clinical, preoperative or postoperative chest CT findings or post therapeutics RAI-131 ablation whole-body scans (Song H.J., 2015). Study done by Kim H. *et al* (2018) found that at initial presentation, 62% patient had only lung metastasis, 20% had only bone metastasis and 18% had combined lungs and bone metastasis. About 50% of patients with lung metastases died within 10 years and respiratory failure were the most common cause of death (Song H. J. *et al*, 2015). FTC has poorer prognosis compared to that of PTC (Jeon M. *et al*, 2018). Therefore, more aggressive and repeated RAI-131 therapies are given to the patients with lung metastases as long as iodine avidity is presence (Kwong N. *et al*, 2014).

1.1.6 **Management**

For about seven decades, thyroid cancer patients who are proven by biopsy have been recommended for surgical thyroidectomy, remnant RAI-131 ablation and followed by thyroid hormone suppression therapy (Kwong N. *et al*, 2014). The initial treatment for patients with thyroid cancer with the size of at least 1cm is to remove the primary tumour with the affected thyroid lobe by undergoing total or near total thyroidectomy. Therapeutic lymph node dissection would be performed on patient whose lymph node involvement is evident clinically on ultrasound and lymph node Fine Needle Aspiration Cytology (FNAC). This may reduce the risk of recurrence and to enable the RAI therapy (Haugen B.R. *et al*, 2015; Sosa *et al*, 2006). PTC tends to spread via lymphatic chain while FTC via blood vessels.

The remnant RAI ablation is an attempt to destroy any residual normal thyroid tissue or known macroscopic thyroid cancer post-surgery. A high-risk patient will receive remnant RAI ablation following surgery while it is not necessary for a low-risk patient. RAI may be indicated for an intermediate risk patient.

Removal of thyroid gland in a patient will also cause drop of thyroid hormone (T4 and T3) level and cause rising of his/her thyroid stimulating hormone (TSH) level. The increased TSH may promote growth of any potential residual tumour cells. By giving thyroid hormone replacement therapy (levothyroxine) to the patient, it can suppress the TSH level. The patient must be supplied with this thyroid hormone replacement therapy for the rest of his/her life.

Serum Tg should be undetectable post total thyroidectomy. Presence of serum Tg level may indicate presence of residual or recurrence thyroid cancer cell. Thus monitoring of serum Tg as a tumour marker is crucial (Haugen B.R. *et al*, 2015, F. Pacini *et al* 2002).

Based on post RAI ablation whole body scan, the lung metastases were classified into iodine avid and non iodine avid. The iodine avid has functioning lung metastasis while the non iodine avid has non functioning lung metastasis. The benefit of radioiodine ablation is very limited for non iodine avid lung metastases (Song H.J., 2015). 70% of patients with lung metastases are iodine avid. Several studies found that patients with iodine avid lung metastases had longer survival rates compared to the non iodine avid lung metastatic patients. Iodine avid DTC patients with lung metastasis have longer survival rates than those with non iodine avid metastasis, 60% and 10%, respectively (Jang E.K *et al*, 2015). Most iodine avid lung metastasis DTC patients obtained partial or complete remission about 60% and 24%, respectively, with significant decrease of serum Tg level. They also had reduction in pulmonary metastases on follow up CT (Song H. J. *et al*, 2015).

1.2 Radioiodine (RAI) Therapy

Radioiodine (RAI) or Iodine-131 (^{131}I) was first introduced as an oncologic therapeutic agent in the early 1940s. And now after 80 years, Iodine-131 is available in many centres and has become the main mode of treatment.

Iodine-131 is formed from fission of uranium and can be produced in a reactor. It then decays into Xe-131 by emitting Beta (β) and Gamma (γ) rays. The β-ray has maximum energy of 0.61MeV (89% abundance) with an average energy of 0.192MeV. The β-ray will be emitted into the soft tissue with mean range of 0.4mm and can go up to 0.8mm in the tissue (Mumtaz M. *et al*, 2009). This high energy of β-ray is not for imaging but is valuable for therapy (Lin *et al*, 2015). Meanwhile, the γ-ray has 0.364MeV (81% abundance) and used for imaging and localization as well as calculation of the radioiodine thyroid uptake ratio (Bonnema *et al*, 2012). It has physical half-life of eight days and effective half-life of six days (Cepkova *et al*, 2014). Remnant RAI ablation successful rate is quite high and about 70% of loco-regional lymphadenopathies and pulmonary micrometastasis are cured (Haugen B.R. *et al*, 2015; F. Pacini *et al*, 2012).

Within 1 hour of Iodine-131 ingestion, iodine will be reduced to iodide in the small bowel and will enter blood circulation. The follicular cell of the thyroid traps iodide via iodide simporter and then organifies the iodide. Iodide will be concentrated up to 500 times greater than plasma level. After that, iodide undergoes oxidization, iodination, coupling and is stored in the colloid cells (Ziessman *et. al*, 2013). RAI-131 emits high energy of β-ray, which causes damage of DNA directly, and indirectly by formation of free radical. This will result in apoptosis or damage of the residual thyroid tissue with little damage to other tissues.

There is no dose limit for Iodine-131 administration by the International Atomic Energy Agency (IAEA) and International Commission on Radiological Protection (ICRP). In general, the dose of Iodine-131 is 1.1-11.1GBq which is equal to 30-300mCi. The maximum permissible dose is limited by the absorbed dose of Iodine-131 to the bone marrow and also its retention in the lung. (Ravichandran *et al*, 2014, Willegaignon *et al* 2006). In recent years, DTC treatment has become more conservative with less extensive surgery, reduced Iodine-131 usage and with lesser follow up for low and intermediate risk patients (Lamartina L. *et al*, 2018)

However, radiation released from Iodine-131 could give early and late complications. Early complications include sialadenitis, xerostomia, worsening swelling of tumour, radiation thyroiditis and gastritis. On the other hand, late complications include chronic sialadenitis and xerostomia, secondary malignancy, radiation cystitis and transient infertility (Ziessman *et al*, 2013).

The risks of radiation pneumonitis and lung fibrosis are raised for patients who receive multiple Iodine-131 in a short interval or large administered activities of Iodine-131 in diffuse lung metastasis DTC. Radiation-induced pulmonary fibrosis was reported about 1-7% in DTC patients with lung metastases after receiving Iodine-131 ablation (Jang E.K, *et al*, 2015). Respiratory complication may be avoided if limiting Iodine-131 with bo dy retention at 48hours is less than 80mCi (Cho S.W. *et al*, 2014). Pre-treatment with administration of corticosteroid may minimise the complication (Richard T.K. *et al*, 2001).

1.3 Pulmonary Function Test

A good pulmonary function could be more important for quality of life in DTC patients due to its relatively longer survival rate as compared to other cancers. As to date, there is only one study done on changes in serial pulmonary function test before and after multiple Iodine-131 ablations in Korea by Jang E.K *et al* (2015). The study found that severe impairment of pulmonary function was observed in 16% of DTC after a median of 3 Iodine-131 ablations. A few risk factors affecting the pulmonary function include elderly, respiratory symptoms, mild impairment baseline and progressive diseases. To date, there is no local data on assessing pulmonary function test among DTC patients that had treatment with radioiodine-131.

Pulmonary function tests (PFTs) are a tool to assess the function of the lung, chest wall and respiratory muscle. It includes a variety of tests which examine the performance of the lungs. It is used to establish the pulmonary function's baseline, evaluates symptoms, detection of pulmonary disease, evaluate pulmonary impairment, operative risk and surveillance for occupational-related pulmonary disease.

The most basic test is spirometry as it is simple and quick procedure. It measures the amount of air in the lungs can hold as well as measures how forcefully one can empty air from the lungs. As for that, spirometry is used to screen for disease that affect lung volumes and disease that affect the airway. Abnormal pulmonary function can be divided into obstructive abnormality or restrictive abnormality (Jang E. K. *et al*, 2015). For example, an obstructive abnormality can be seen in patients with asthma and COPD while restrictive abnormality can be seen in patients with interstitial fibrosis and chest wall deformities.

Guidelines for performing and interpreting PFT have been published by the European Respiratory and American Thoracic Societies (Ranu H. *et al,* 2011). Pulmonary function is measured based on forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC (%). An obstructive pulmonary function is defined as FEV1 is reduced more than FVC, FVC ≥80% and FEV1/FVC <70% and restrictive pulmonary function is defined as FVC is reduced, FVC <80% and FEV1/FVC ≥70%. (Ranu H. *et al,* 2011, Jang E. K. *et al*, 2015). Flow volume loop is generated from the reading when patient performs a maximal inspiratory manoeuvre and followed by a maximal expiratory manoeuvre (Ranu H. *et al,* 2011). This flow volume loop is helpful in interpreting PFT.

Diffusing capacity of the lungs for carbon monoxide (DLCO) is a test to measures the ability of a gas to go from the air sacs into the blood stream. It gives important information regarding the integrity of the pulmonary vascular bed and alveolar membrane (Ranu H. *et al,* 2011). The spirometry is to differentiate an obstructive abnormality from a restrictive abnormality and DLCO gives a clue as to what disease process within that category is present. A low DLCO can be seen in both emphysema and interstitial fibrosis. In restrictive pulmonary function, interstitial fibrosis may cause a low DLCO but chest wall deformities would not.

Baseline and serial pulmonary function tests might be considered for some high risk patients during follow up. It may be crucial for tracking pulmonary disease, quantifying responses to therapy, and early diagnoses of pulmonary injury after exposure to radiation therapy. It also can guide decisions regarding further treatment and intervention.

2.0 RATIONALE/BENEFITS OF THE STUDY

This study is conducted to determine the role and significance of the usage of PFT in assessing pulmonary function in thyroid cancer patients who receive Iodine-131 ablation. It may be crucial for tracking early diagnosis of pulmonary injury after exposure to radioiodine. PFT is done to quantitatively measure lung function before and after the Iodine-131 ablation. It is also to identify clinical factors associated with impaired pulmonary function. By identifying the risk factor, baseline of pulmonary function and impairment of pulmonary function detection on serial assessment of an identified patient, these could possibly change the management plan and increase the quality of the patients' life. Nevertheless this study is also to establish local data regarding changes in pulmonary function for patients with serial PFT.

2.1 Aim

To evaluate changes in pulmonary function of DTC patients after exposure to first Iodine-131 ablation and to look for differences between patients with or without lung metastasis.

2.2 Objectives

2.2.1 General Objective

- To identify the changes in PFT of DTC patients post first Iodine-131 ablation

2.2.2 Specific Objective

- To determine the relationship between PFT and Iodine-131 ablation for DTC patients
- To compare changes in PFT after first Iodine-131 ablation for patients with and without lung metastasis
- To identify significant risk factor affecting PFT in post first Iodine-131 ablation

2.3 Hypothesis Statement

- Null hypothesis: There is no significant worsening in PFT of DTC patients after first Iodine-131 ablation
- Alternative hypothesis: There is significant worsening in PFT of DTC patients after first Iodine-131 ablation

3.0 METHODOLOGY

3.1 Study Design, Study Location and Study Period

A prospective observational study was conducted in Hospital Pulau Pinang involving the Nuclear Medicine Department and Chest Clinic, Medical Department from the period of September 2016 until August 2018 with patient recruitment from September 2016 until January 2018.

3.2 Study Sample

Patients with thyroid cancer who underwent total thyroidectomy and underwent RAI ablation in Peninsular Malaysia were the population of reference. Thyroid cancer patients who were referred to the Nuclear Medicine Department, Hospital Pulau Pinang for RAI ablation were the source population. Hospital Pulau Pinang is a government hospital based in the northern part of Peninsular Malaysia. The Nuclear Medicine Department receives RAI ablation referrals from the states in the northern region of Peninsular Malaysia including Penang, Kedah, Perlis as well as Northern Perak. Patients who came for their first Iodine-131 ablation in the Nuclear Medicine Department, Hospital Pulau Pinang were the sampling population. The study participants were those who had given consents to participate in this study and also fulfilled all the inclusion and exclusion criteria.

Refer APPENDIX B for sample size calculation.

3.3 Inclusion and exclusion Criteria

3.3.1 Inclusion Criteria

- Adult thyroid cancer patient with age more than 18 years old
- Patient who underwent total or near total thyroidectomy (including completion thyroidectomy)
- HPE: confirmed DTC
- Patient who received their first Iodine-131 ablation
- Patient with/without underlying respiratory disease

3.3.2 Exclusion Criteria

- Patient who were pregnant or breastfeeding
- Patients who had received RAI ablation before

3.4 Data Collection

3.4.1 Patient selection and preparation before Iodine-131 ablation

All DTC patients who were referred to Nuclear Medicine, Hospital Pulau Pinang for their first Iodine-131 ablation were required elective admission to the ward. Dates for admission, explanation and a copy of the leaflet from Nuclear Department regarding the instruction and list of preparation for Iodine-131 ablation were given to the patients by the

referring team (APPENDIX C). This preparation was to ensure the effectiveness of Iodine-131 ablation.

A reminder and further explanation on the preparation were given to the patients via phone call a few weeks before treatment. Patients were instructed to withhold Tab. L-Thyroxine and iodine containing medicines or supplements for 4 weeks prior to admission. Patients also were advised to avoid high iodine containing food 2 weeks prior to admission such as seafood and sea salt.

Early in the morning on the day of the admission, all patients were clerked and examined to ensure they were in compliance to the preparation. Blood was taken to check for stimulated TSH and baseline stimulated serum Tg. The patients were screened by the Principal Investigator (PI) and those who fulfilled the inclusion criteria were selected to be part of this study. All participants were given counselling and were informed on the consents by the PI. Clinical data and written consents were obtained (APPENDIX D and E).

Refer APPENDIX A for study flow chart.

3.4.2 **Baseline Pulmonary Function Test (1st PFT)**

In the morning, participants were sent to the Chest Clinic, Medical Department, Hospital Pulau Pinang after ward admission for their first PFT as a baseline reading. In the afternoon, Iodine-131 (80-150mCi) was given to the participants orally and they were warded for 4-5 days in isolation. The low risk group received 80mCi, the intermediate risk group with no evidence of metastasis to the lymph node received 100mCi, while the

intermediate risk group with evidence of metastasis to lymph node received 120mCi. 150mCi was given to the high risk group which presented with metastasis.

Whole body scan (WBS) was performed 4-5 days after Iodine-131 ingestion using gamma camera. Images were obtained to detect remnant of thyroid tissue in the neck and any distant metastasis. Planar image of whole body were acquired at table rate of 10cm/min and spot view of neck were acquired for 480 seconds using gamma camera (Siemen), High Energy General purpose (HEGP) collimator and 20% window was set at the peak energy of 360keV.

WBS post ablation and CT scan of lung (for positive uptake) is a standard procedure (any patient outside of this study would still need to undergo this procedure if necessary). Participants' staging were based on their histopathological examination (HPE) findings, radiological imaging (CT scan) and post RAI ablation WBS. Presence of local lymph node can be observed via HPE findings and CT scan while mediastinal or distance lymph node can be observed by CT scan or / and post Iodine-131 ablation WBS.

All participants were discharged from the ward after Iodine-131 ablation WBS and external dose rate falls below 50μSv/H *(Atomic Energy Licensing Act 1984, Act 304).*

3.4.3 **Second and Third Pulmonary Function Test (2nd and 3rd PFT)**

All patients were given follow up appointments in the Nuclear Medicine Department for another 3 months (up to 6 months) after first Iodine-131 ablation. Serum Tg and thyroid function test were monitored. They were assessed clinically and monitored biochemically for any possibility of persistent, progressive or recurrence disease. All the

participants went for second PFT in the Chest Clinic on the same day, prior to clinic follow up in the afternoon.

On the 6th month of follow-up, patients with known metastasis either from CT scan or post first Iodine-131 ablation WBS underwent second Iodine-131 ablation. While patients without metastasis underwent first diagnostic WBS with low dose Iodine-131 (5mCi). All participants went for third PFT in the Chest Clinic on the same day and prior to Iodine-131 ingestion in the afternoon.

Any important and relevant clinical parameters were obtained during clinical reviews and were documented in the data collection form (APPENDIX F).

3.4.4 **Pulmonary Function Test Procedure**

Participants were first seated on chairs and were told to breathe normally. They were asked to slowly blow out air until the lungs felt empty. Then they should be taking a big deep breath to completely fill up their lungs (maximal inspiratory manoeuvre). As soon as their lungs felt full, they blew out into the spirometer mouthpiece as hard and fast as they could until they felt their lungs were absolutely empty (maximal expiratory effort). They were required to repeat all the steps for at least 3 times to be sure the results were acceptable and reproducible. This test was conducted by the Medical assistant (MA) in charge of the respiratory clinic.

Several numbers were generated including the FEV1 and FVC. Flow volume loop/curve were generated by those numbers. All the readings were recorded, analysed and interpreted using winspiroPRO HL7 interface specification Ver 1.0 (March 2012) based on

Knudson prediction equation (1983) and American Thoracic Society (ATS) Guideline. The results were validated by respiratory physician.

The PFT machine was calibrated by the MA in charge every other day by using 3 L calibration syringe.

FIGURE 3.1: Spirometer

3.4.5 **Study Outcome**

Participants who had worsening in serial PFT at 3 or 6 months after their first Iodine-131 ablation would demonstrate either one of the outcomes below:

1. From a baseline of normal PFT to mild or moderate or moderately severe abnormal PFT;
2. From a baseline of mild abnormal PFT to moderate or moderately severe abnormal PFT; and
3. From a baseline of moderate abnormal PFT to moderately severe abnormal PFT.

If there is no worsening in serial PFT, the participants would demonstrate either one of the outcomes below:

1. No changes from a normal baseline PFT and serial PFT
2. No changes from a mild abnormal PFT and serial PFT; and
3. No changes from a moderate abnormal PFT and serial PFT.

An abnormal PFT can be divided into restrictive and obstructive. An obstructive pulmonary function is define as an FVC ≥80% and FEV1/FVC <70% and suggestive of restrictive pulmonary function if FVC <80% and FEV1/FVC ≥70%. Restrictive and obstructive pulmonary function can be further divided into mild, moderate, moderately severe, severe and very severe. Grading for obstructive pattern based on FEV1 while restrictive pattern based on FVC (Table 3.1) (Pulmonary Function Test in Clinical Practice by Ali Altalag, 2009).

TABLE 3.1: Severity Grading of Abnormal Pulmonary Function Test

Grading	***FEV1 (obstructive) or FVC (restrictive)***
Mild	≥70%
Moderate	60-69%
Moderately severe	50-59%
Severe	35-49%
Very severe	<35%

3.5 Data Analysis

Statistical analysis were performed using IBM Statistical Package for Social Science software version 19. Descriptive results were expressed as frequency (percentage), mean ± standard deviation for normal data or median (IQR) for skewed data. Comparison between two groups was performed using Chi-square test or Fisher Exact's when correction is needed. The differences between two groups were analysed by using the Mann-Whitney test. The differences between serial pulmonary function test results were analysed by using the Kruskal-Wallis test. P value of 0.05 and less was considered as significant.

3.6 Ethics and Disclosure

This study was in accordance with the ethical standards of Malaysian Guideline for Good Clinical Practice (National Committee for Clinical Research, 2011) as well as the Helsinki Declaration of 1964, revised in 2013 (World Medical Association 2013). This study has been approved by the Medical Research Ethics Committee (MREC) of the Malaysian Ministry of Health and registered with the National Medical Research Register (NMRR-15-2465-28418)(APPENDIX H). This study also has been approved by the Jawatankuasa Etika Penyelidikan Manusia (JEPeM) of Universiti Sains Malaysia (USM/JEPeM/17100428)(APPENDIX I).

Written informed consent was obtained from all study participants prior to the initiation of the study. Confidentiality was strictly maintained, and data was rendered as anonymous except for the purpose of subject identification during statistical analysis. The author has no conflicts of interest to disclose, which may influence the impartiality of this study.

4.0 RESULT

4.1 Demographic Data

A total of 53 participants who were referred for their first Iodine-131 ablation were eligible to be recruited based on inclusion and exclusion criteria. However, only 49 pariticipants were enlisted in this study due to inability of the participants to complete the study due to defaulted follow up.

The median age of the enlisted participants was 42 years old while the youngest was 18 years old and the oldest was 78 years old. Most of them belong to the age group of 21 to 40 years old (Figure 4.1).

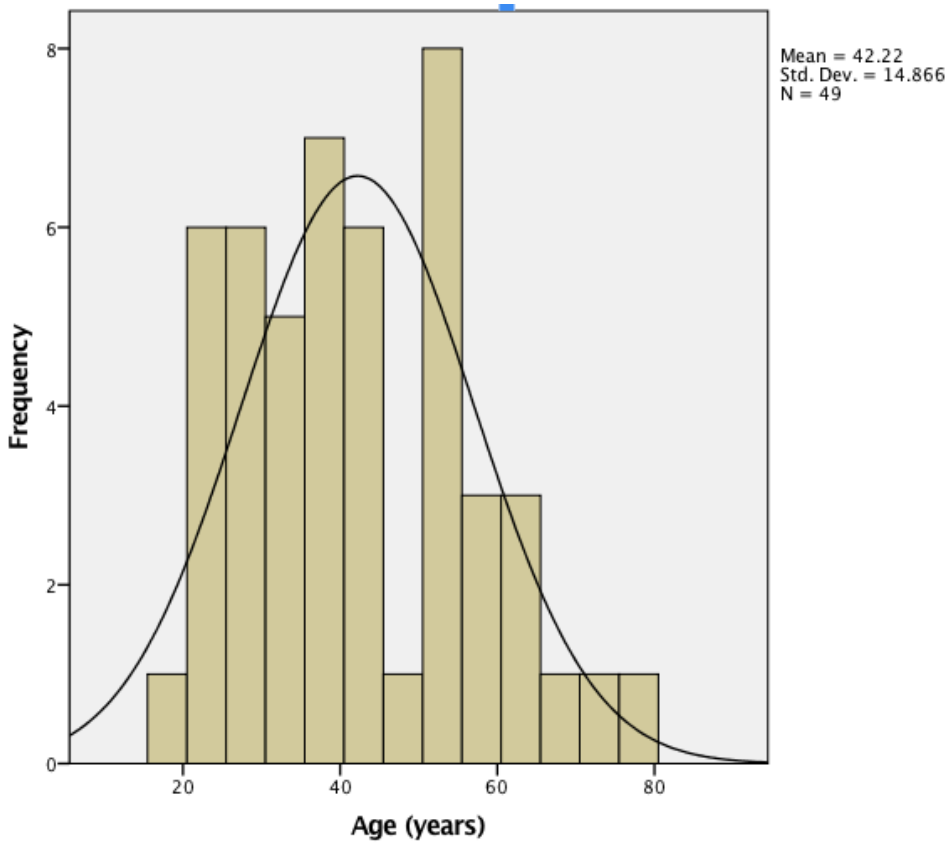

FIGURE 4.1: Age distribution of participants

Based on TNM staging, only nine participants (18%) were more than 55 years old, who were under the high-risk group for recurrence. While majority, 40 participants (82%) were 55 years old or less and they fell under the lower risk group (Figure 4.2).

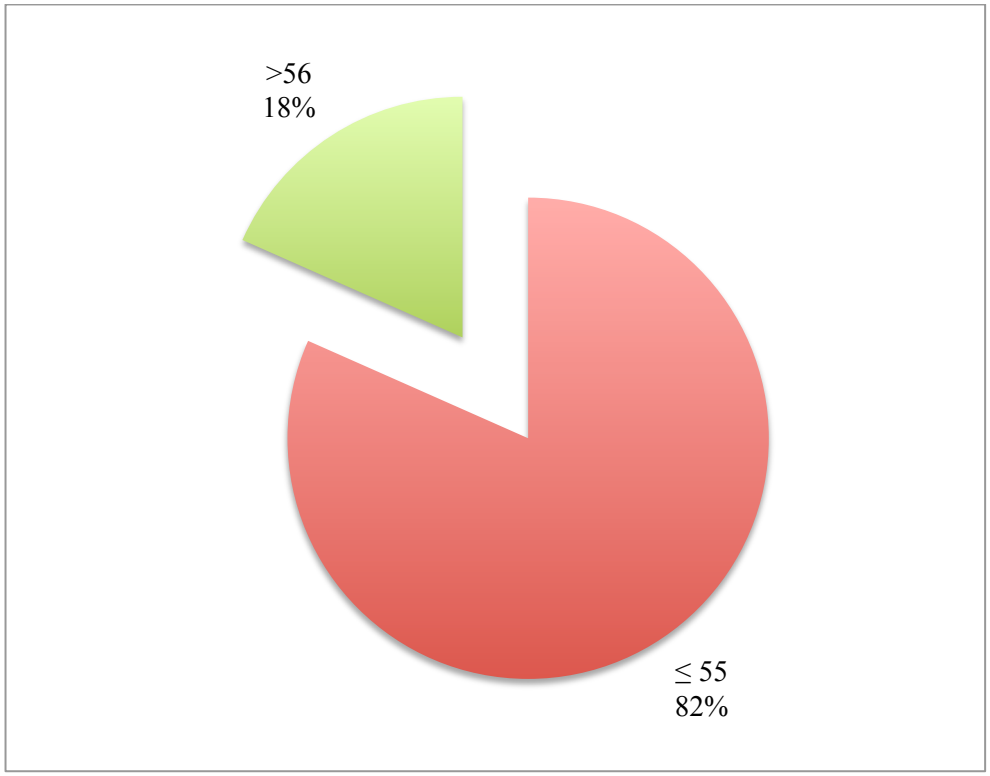

FIGURE 4.2: Age distribution base on TNM staging