



OUTCOME FOLLOWING FIRST RADIOIODINE THERAPY
FOR REMNANT ABLATION OF
LOW-RISK DIFFERENTIATED THYROID CANCER
AT INSTITUT KANSER NEGARA (IKN)

By

DR. ANTHONY LOUIS ANAK KINDU

Department of Biomedical Imaging

Advanced Medical and Dental Institute

Universiti Sains Malaysia

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DECLARATION

I declare that this research has been submitted to Universiti Sains Malaysia (USM) for the Master of Medicine (Nuclear Medicine) program. It has not been forwarded to other universities. Consequently, this research is available for consultation and may be photocopied for reference purposes.

ANTHONY LOUIS ANAK KINDU

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DISCLAIMER

I hereby certify that the work in this dissertation is my own. I declare that I have no financial interest in the instruments or materials used in this study.

ANTHONY LOUIS ANAK KINDU

P-IPM0023/19

Date: 23/11/2023

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TABLE OF CONTENT

	Page
DECLARATION	ii
DISCLAIMER	iii
ACKNOWLEDGEMENT	iv
TABLE OF CONTENT	v
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATION	xi
ABSTRAK	xiii
ABSTRACT	xv
1.0 INTRODUCTION	1
2.0 LITERATURE REVIEW	3
2.1 Differentiated Thyroid Cancer	3
2.1.1 <i>Definitions and Demographics</i>	3
2.1.2 <i>Diagnosis of Differentiated Thyroid Cancer</i>	4
2.1.3 <i>Management of Differentiated Thyroid Cancer</i>	5
2.1.4 <i>Low-Risk Differentiated Thyroid Cancer</i>	6
2.2 First Radioiodine Therapy for Remnant Ablation in Low-Risk Differentiated Thyroid Cancer	7
2.3 Treatment Outcome of First Radioiodine Therapy for Remnant Ablation in Low-Risk Differentiated Thyroid Cancer	8

2.4 Factors Affecting Efficacy of Remnant Ablation in Differentiated Thyroid Cancer	9
2.5 Conclusion	12
3.0 RATIONALE / BENEFITS OF THE STUDY	13
3.1 Aim	13
3.2 Objectives	14
3.2.1 General Objectives	14
3.2.2 Specific Objectives	14
3.3 Hypothesis Statements	14
4.0 METHODOLOGY	15
4.1 Study Design, Study Location and Study Period	15
4.2 Study Sample	15
4.3 Sample Size Calculation	16
4.4 Inclusion And Exclusion Criteria	18
4.4.1 Inclusion Criteria	18
4.4.2 Exclusion Criteria	18
4.5 Criteria for Successful Remnant Ablation	19
4.6 Data Collection	20
4.7 Data Analysis	21
4.8 Ethics And Disclosure	22

5.0 RESULTS	23
5.1 Demographic and Clinical Data	23
5.2 Determination of TSH-stimulated serum Thyroglobulin Cut-Off Value	26
5.3 Treatment Outcome and Factors Affecting Successful Remnant Ablation in Low-Risk Differentiated Thyroid Cancer	28
5.4 Independent Affecting Factors for Successful Remnant Ablation in Low-Risk Differentiated Thyroid Cancer	32
6.0 DISCUSSION	33
6.1 Treatment Outcome of Remnant Ablation in Low-Risk DTC at Institut Kanser Negara	33
6.2 Primary Tumour Size as A Risk Factor for Unsuccessful Remnant Ablation in Low-Risk Differentiated Thyroid Cancer	37
6.3 Pre-Ablation sTg as a Predictor of Successful Remnant Ablation in Low-Risk Differentiated Thyroid Cancer	38
6.4 Effect of Pre-Ablation CECT on Treatment Outcome	40
6.5 Impact of Delayed Remnant Ablation Towards Unsuccessful Treatment Response in Low-Risk Differentiated Thyroid Cancer	42
6.6 Other Confounding Factors That Favor Successful RRA in Low-Risk Differentiated Thyroid Cancer	44
7.0 LIMITATIONS	46
8.0 CONCLUSION	48

9.0 RECOMMENDATIONS	49
REFERENCES	50
APPENDICES	
APPENDIX A: Three-tiered risk stratification of Differentiated Thyroid Cancer	61
APPENDIX B: Conceptual Framework of Study	62
APPENDIX C: Treatment Response in Differentiated Thyroid Cancer post-TT and Radioiodine Remnant Ablation	64
APPENDIX D: Patient Information Sheet	65
APPENDIX E: Medical Research and Ethics Committee Approval Letter	66
APPENDIX F: JEPeM Approval Letter	69

LIST OF TABLES

- Table 1: Baseline characteristics of study population**
- Table 2: AUC for ROC analysis of pre-ablation endogenous TSH-stimulated serum thyroglobulin (sTg)**
- Table 3: Patient characteristics based on the calculated sTg cut-off value generated from ROC graph**
- Table 4: Comparison of two groups in patient with low-risk differentiated thyroid cancer in relation to the affecting factors towards treatment outcome**
- Table 5: Multivariate logistic regression analyses to identify independent affecting factors of successful remnant ablation in low-risk differentiated thyroid cancer**

LIST OF FIGURES

Figure A: ROC curve of pre-ablation endogenous TSH-stimulated serum Thyroglobulin in low-risk differentiated thyroid cancer in discriminating successful and unsuccessful remnant ablation

Figure B: Outcome following radioiodine therapy for remnant ablation of low-risk differentiated thyroid cancer at Institut Kanser Negara

LIST OF ABBREVIATION

ACR	American College of Radiology
AJCC	American Joint Committee of Cancer
anti-TgAb	Anti-thyroglobulin antibody
ATA	American Thyroid Association
ATA guidelines 2015	ATA Management Guidelines for Adult Patients with Thyroid Nodules and DTC 2015
AUC	Area under the curve
CECT	Contrast-enhanced computed tomography
DTC	Differentiated thyroid carcinoma
EANM	European Association of Nuclear Medicine
FNA	Fine needle aspiration
FTC	Follicular thyroid carcinoma
FVPTC	Follicular variant papillary thyroid carcinoma
HPE	Histopathological examination
I-123	Iodine-123
I-131	Iodine-131
I-WBS	Iodine whole body scan
ICA	Iodinated contrast agent
IKN	Institut Kanser Negara
JEPeM	Jawatankuasa Etika Penyelidikan Manusia USM
JPN	Jabatan Perubatan Nuklear
LID	Low-iodine diet
MBq	megaBecquerel

mCi	milliCurie
MNCRR	Malaysia National Cancer Registry Report
MREC	Medical Research & Ethics Committee
NIS	Sodium iodide symporter
NMRR	National Medical Research Register
OR	Odd ratio
PTC	Papillary thyroid carcinoma
RAIT	Radioactive iodine therapy
ROC	Receiver operating characteristic
RRA	Remnant radioiodine ablation
sTg	TSH-stimulated serum thyroglobulin
Tg	Thyroglobulin
TIRADS	Thyroid Imaging Reporting & Data System
TNM	Tumour, Nodes, Metastasis
TSH	Thyrotrophin
TT	Total thyroidectomy
UIC	Urine iodine concentration
USM	Universiti Sains Malaysia

ABSTRAK

Pengenalan: Pemberian rawatan radioiodin dalam kalangan pesakit kanser tiroid berisiko rendah post-tiroidektomi total merupakan isu perdebatan yang hangat di kalangan pakar perubatan. Kadar kematian untuk kanser tiroid adalah rendah iaitu kurang daripada 1% dan kadar penyakit kekal atau berulang juga dilaporkan rendah iaitu 2% - 3%, rawatan radioiodin terhadap pesakit-pesakit ini masih menjadi tanda persoalan sama ada untuk dirawat dengan radioiodin mahupun tidak. Kajian ini bertujuan untuk melihat kadar peratus keberkesanan rawatan radioiodin di dalam kalangan pesakit kanser tiroid berisiko rendah post-tiroidektomi total dan seterusnya meneliti faktor-faktor yang boleh mempengaruhi kadar peratus keberkesanan rawatan yang diberikan.

Metodologi: Kajian ini merupakan kajian retrospektif yang terdiri daripada sejumlah 212 pesakit kanser tiroid berisiko rendah yang telah diberikan rawatan radioiodin dengan aktiviti iodin-131 100 milliCurie (mCi) dan ke bawah sepanjang Januari 2017 sehingga Disember 2020 di Jabatan Perubatan Nuklear, Institut Kanser Negara (JPN, IKN) dengan pelbagai faktor yang telah dikenalpasti mungkin akan mempengaruhi kadar keberkesanan rawatan yang telah diberikan. Rawatan diklasifikasikan sebagai berjaya sekiranya imej diagnostik radioiodin-131 (I-131) seluruh badan adalah negatif berserta nilai serum tiroglobulin dirangsang tirotrofin endogen adalah <1.0 ng/mL secara dua kali berturut selama tempoh rawatan susulan pada 6 sehingga 12 bulan selepas pemberian rawatan radioiodin. Nilai pemotongan untuk sTg ditentukan menggunakan keluk cirian operasi penerima. Faktor-faktor risiko yang boleh mempengaruhi kadar keberkesanan rawatan radioiodin dianalisa menggunakan univariat dan multivariat logistik regresi.

Keputusan: Kadar peratusan keberkesanan rawatan radioiodin di kalangan kanser tiroid berisiko rendah di IKN adalah 56.6%. Laras nilai untuk serum tiroglobulin dirangsang tirotrofin endogen adalah 5.96 ng/mL dengan 66.0% sensitif, 68.8% spesifik, 81.5% nilai prediksi positif dan 66.9% kejituan dalam penentuan keberkesanan rawatan radioiodin dalam kalangan pesakit kanser tiroid berisiko rendah post-tiroidektomi total. Merujuk kepada analisa univariat, kumpulan pesakit berumur 55 tahun ke bawah ($p = 0.037$), tidak mempunyai metastasis kelenjar limfa ($p = 0.023$), dan nilai serum tiroglobulin dirangsang tirotrofin endogen <5.96 ng/mL ($p = 0.000$) merupakan antara faktor yang dikenalpasti menyumbang kepada meningkatnya keberkesanan rawatan radioiodin dalam kalangan pesakit kanser tiroid berisiko rendah post-tiroidektomi total. Melalui analisa multivariat logistik regresi, pesakit yang berumur 55 tahun ke bawah ($p = 0.018$, OR 5.130), tidak mempunyai metastasis kelenjar limfa ($p = 0.038$, OR 6.207) dan pesakit yang mempunyai nilai sTg <5.96 ng/mL ($p = 0.000$, OR 3.929) adalah merupakan tiga faktor utama yang memberi implikasi besar terhadap kadar keberkesanan rawatan radioiodin dalam kalangan pesakit kanser tiroid berisiko rendah post-tiroidektomi total di IKN.

Kesimpulan: Kadar peratusan keberkesanan rawatan radioiodin dalam kalangan kanser tiroid berisiko rendah di IKN adalah 56.6%. Pesakit yang berumur 55 tahun ke bawah, tidak mempunyai metastasis kelenjar limfa serta mempunyai nilai sTg <5.96 ng/mL merupakan tiga faktor utama yang dikenalpasti menyumbang kepada peningkatan kadar keberkesanan rawatan radioiodin di kalangan pesakit kanser tiroid berisiko rendah post-tiroidektomi total.

ABSTRACT

Purpose: The role of remnant radioiodine ablation (RRA) in post-total thyroidectomy low-risk differentiated thyroid cancer (DTC) has been a debatable issue among experts over the decades. Given that the risk of disease-specific death is less than 1% as well as only 2% - 3% risk of persistent or recurrent disease in low-risk DTC, the role of giving radioactive iodine therapy (RAIT) remains in the grey area. This study is to evaluate the outcome of RRA in low-risk DTC and to identify the possible affecting factors that may result in unsuccessful RRA in low-risk DTC.

Methodology: A retrospective study of 212 patients with low-risk DTC treated with radioiodine-131 (I-131) with activities of 100 mCi and below from January 2017 to December 2020 at Nuclear Medicine Department, Institut Kanser Negara (IKN) with varying factors were identified to determine outcome following RRA in our centre. The outcome of a successful RRA was determined by negative diagnostic radioiodine-131 whole body scan (I-131 WBS) and endogenous thyrotrophin-stimulated serum thyroglobulin of (sTg) <1.0 ng/mL at two consecutive follow-up 6 to 12 months after RRA. sTg cut-off value was determined by using receiver operating characteristic (ROC) curve. The association of risk factors that may affect the successful RRA in low-risk DTC were determined using univariate and multiple logistic regression analysis.

Results: The successful rate of RRA in low-risk DTC in IKN is 56.6%. The cut-off value of sTg is 5.96 ng/mL with 66.0% sensitivity, 68.8% specificity, 81.5% positive predictive value, and 66.9% accuracy in predicting successful RRA. In univariate analysis, the significant predicting factors for successful RRA in low-risk DTC are age group of below 55-years-old ($p = 0.037$), absent of lymph node metastasis ($p = 0.023$), and pre-ablation sTg of <5.96 ng/mL ($p = 0.000$). In multivariate analysis, it was found that patients aged below 55-years-old ($p = 0.018$, OR 5.130), absent of lymph node metastasis ($p = 0.038$, OR 6.207) and pre-ablation sTg of <5.96 ng/mL ($p = 0.000$, OR 3.929) were found to be the independent risk factors that has good association towards successful remnant ablation in low-risk DTC in IKN.

Conclusion: The successful outcome of RR in low-risk DTC in IKN was 56.6%. Patients aged below 55-years-old, absent of nodal metastasis and pre-ablation sTg of <5.96 ng/mL are three independent factors in prediction of successful RRA in low-risk DTC.

1.0 INTRODUCTION

Differentiated thyroid cancer (DTC) is characterized as a malignancy arising from the follicular epithelium with the preservation of the physiological cellular characteristics of thyroid follicles in expression of the sodium iodide symporter (NIS) which is the primary cellular feature responsible for the specific iodine uptake (1, 2). DTC encompasses more than 90% of overall thyroid malignancies which are further subdivided into three major categories: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hurthle cell carcinoma with the incidence of 80% - 85%, 10% - 15% and 3% - 4% respectively (3). From a report by Malaysia National Cancer Registry Report (MNCRR) 2012 – 2016, thyroid cancer is the eighth commonest cancers among the female population with the crude incidence rate of 3.2. It is more prevalent amongst Malays followed by Indians and Chinese of Malaysian female population (4).

The standardised and established therapeutic options for DTC still remains as surgery and radioactive therapy (RAIT), subsequently by thyrotropin suppression therapy via levothyroxine (5). Post-total thyroidectomy (TT), it is essential to evaluate and stratify the patient's risk in order to predict the likelihood of disease recurrence and/or persistence. Based on American Thyroid Association (ATA) guidelines 2015 on management of thyroid nodules and DTC, the initial risk stratifications are classified into three tiers; low-, intermediate-, and high risk (6).

Remnant ablation in post-TT low-risk DTC has been a debatable issue among the experts over the decades. Giving that less than 1% of the risk of disease-specific death in addition to risk of persistent or recurrent disease in low-risk DTC of only 2% - 3%, its

role remains in the grey area (6). However, there are still no available up to date guidelines that can scrutinize the role of remnant ablation in post-total thyroidectomy DTC. By definition, remnant ablation signifies the utilisation of I-131 to abolish post-operatively presumed remaining benign thyroid tissue to aid the initial staging and during the follow-up periods (2). It has widely been acknowledged that the first activity of I-131 given post-TT can be used for the effort to abolish the remnant presumably benign thyroid tissue (remnant ablation), suspected but unidentified disease residual (adjuvant radioiodine therapy)/or known remaining or recurrent disease (6).

The goal of this study is to determine the successful rate of first RAIT of low-risk DTC at Institut Kanser Negara (IKN) and to identify the possible risk factors that may result in poor outcome of the therapy in this centre.

2.0 LITERATURE REVIEW

2.1 Differentiated Thyroid Cancer

2.1.1 Definition and Demographics

DTC encompasses more than 90% of overall thyroid malignancies. Three major categories of DTC are PTC with the incidence of 80% - 85%, followed by FTC with 10% - 15% of incidence and the remaining 3% - 4% of cases are from Hurthle cell carcinoma (1). DTC is characterized as malignancy arising from the follicular epithelium with the preservation of the physiological cellular characteristics of thyroid follicles in the expression of NIS which is the mainstay features for specific iodine uptake (2). This in turn brought the use of RAIT in thyroid cancer since 1940s (3). The incidence of DTC over the decades has increased with the prevalence found to be higher in females compared to males up to 2.5 to 3 times (5).

2.1.2 Diagnosis of Differentiated Thyroid Cancer

In accordance with ATA guidelines 2015, combination of both radiologic and pathologic modalities is crucial to diagnose DTC. Individual with suspected thyroid nodule, nodular goitre, or thyroid incidentalomas detected on other imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) or focal thyroid uptake on 18-Flourine-Fluorodeoxyglucose (18F-FDG) are warranted for diagnostic thyroid or neck ultrasonography (USG) to further characterize the nodule (6). A well-established American College of Radiology (ACR) proposed thyroid imaging reporting and data system (TI-RADS) published in 2017 by Tessler *et al* is being diversely used in characterization of the thyroid nodule. The nodule is assessed for its composition, echogenicity, shape, margin as well as echogenic foci which at the end will categorize the patient from TI-RADS 1 to 5. TI-RADS 5 shows highly suspicious features on sonography and carries 70% - 90% risk of overall malignancy, thus merited for further histopathological examination via fine needle aspiration (FNA) cytology (6, 7).

Bethesda system for reporting thyroid cytopathology has become a universal diagnostic tool to classify the cytological specimen obtained from FNA. It is classified into 6 categories: I = non-diagnostic or unsatisfactory specimen; II = benign; III = atypia of undetermined significance or follicular lesion of undetermined significance; IV = follicular neoplasm or suspicious for a follicular neoplasm; V = suspicious of malignancy; VI = malignant. Each of the categories carries the estimated risk of malignancy of 1% - 4%, 0% - 3%, 5% - 15%, 15% - 30%, 60% - 75%, and 97% - 99% respectively (8).

2.1.3 Management of Differentiated Thyroid Cancer

The standardized and established therapeutic option for DTC is remained as surgery by the mean of either total or near-TT followed by RAIT in selected patients, subsequently by TSH suppression therapy using levothyroxine (5, 9). Post-operatively, the tumour, nodal, and metastatic (TNM) status of DTC is assessed as per American Joint Commission on Cancer (AJCC) 8th edition to properly stage the patient which enable the health care professionals to give an accurate patient's risk-stratified descriptions as it will provide the prognostic information. Apart from that, it also works as an adjunct for clinicians in deciding on either surveillance or therapeutic strategies for individualised patient's standard of care (6, 10).

2.1.4 Low-Risk Differentiated Thyroid Cancer

The ATA guideline 2015 has been vastly used and recommended for post-thyroidectomy risk stratification in DTC patients. Patients are classified as having low, intermediate, or high risk of recurrence based on the three-tiered clinico-pathologic risk stratification. The risks of recurrence in reported literatures for each of the category are 3% - 13%, 17% - 45%, and 60% - 85% respectively (6, 11).

PTC with no evidence of local or distant metastases, non-aggressive histology, no vascular invasion, clinically no regional or five-or-less pathologic regional nodal metastasis measuring less than 0.2 cm in largest diameter, intrathyroidal encapsulated follicular variant of PTC (FVPTC), and unifocal intrathyroidal papillary microcarcinoma are classified as low-risk DTC. Apart from that, FTC with capsular invasion and no or less than 4 foci of vascular invasion is also categorised at low-risk DTC (6). Appendix A shows the overall three-tiered risk stratification.

2.2 First Radioiodine Therapy for Remnant Ablation in Low-Risk Differentiated Thyroid Cancer

Remnant radioiodine ablation (RRA) with radioiodine-131 (I-131) post-TT in DTC now became a standard practice even when there are no proven facts of metastasis and without a definitive selection of patient based on risk factors (2). By definition, remnant ablation signifies the utilisation of I-131 in eliminating post-operatively presumed remaining benign thyroid tissue, suspected but unidentified disease residual and/or known remaining or recurrent disease to aid the initial staging and follow-up studies (12, 13). For this, the afore-mentioned risk stratification is paramount.

Recently published Estimab12 study in 2021 by Leboulleux et al regarding the need for RAIT in low-risk DTC showed group of patients on a follow-up strategy showed no significant differences in term of disease event recurrence compared to those receiving remnant ablation group (14). Having said that, role of remnant ablation in post-TT low-risk DTC is still debatable, albeit no up-to-date guidelines against its utility in low-risk DTC (4, 15).

According to ATA guidelines 2015, the roles of RRA in post-TT low-risk DTC remain applicable, contingent on the decisions of healthcare professionals. These decisions take into account patient risk factors and preferences (6). It is advisable to minimize the I-131 activity administered to selected patients undergoing RRA to mitigate unnecessary radiation exposure (16).

2.5 Treatment Outcome of First Radioiodine Therapy for Remnant Ablation in Low-Risk Differentiated Thyroid Cancer

In the assessment of treatment outcomes following RAIT therapy in DTC, ATA guideline 2015 has introduced three-tiered categories which can be classify as either excellent, indeterminate, or incomplete (biochemical or structural) responses. Excellent treatment response is defined as negative I-131 imaging post-RAIT with suppressed serum thyroglobulin of less than 0.2 ng/mL or TSH-stimulated serum thyroglobulin (sTg) of less than 1 ng/mL. It has been acknowledged and validated as a more objective system for ongoing therapy response evaluation, providing a reflection of the clinical outcome (6).

The reported successful rate of remnant ablation of low- to intermediate-risk DTC among Asian populations are ranging from 55.6% - 84.2% (16 – 21). In view of wide range successful rate of RRA DTC among the Asians, there are several reported literatures on the factors affecting the efficacy of the RRA in DTC namely by Ha *et al*, Liu *et al*, Wang *et al*, Li *et al*, as well as Claimon *et al* (16, 22 – 25).

2.4 Factors Affecting Efficacy of Remnant Ablation in Differentiated Thyroid Cancer

There are multifactorial causes that may affect the outcomes of RRA in DTC. The most identified risk factors such as TNM status upon diagnosis as well as the duration of RRA post-TT have been vastly reviewed in literature. Nonetheless, high level of sTg pre-ablation also has been widely acknowledged as poor prognostic factor towards outcome of RRA in DTC (26 – 29). Apart from that, the use of contrast-enhanced computed tomography (CECT) one month prior to RAIT also has been shown to reduce the efficacy of RAIT in DTC (30 – 32).

The tumour size (T status) of DTC can be classified into six sub-groups based on the latest 8th edition of AJCC which are Tx, T0, T1, T2, T3 and T4. In low-risk DTC, the tumour size can be more than 4cm in size however, the tumour must still be limited to the thyroid gland itself and classify as T3a tumour (6, 10). In a study done by Wang *et al*, median primary tumour measured 1.7 cm and above was found to be significant, resulting in unsuccessful RRA in DTC (23). The outcome is even poorer if the primary tumour is regarded as T2 and above; size of 2.0 cm and more (22).

The designation of sTg as the primary biochemical tumour marker in patients diagnosed with DTC over the last few decades has played a pivotal role. Its significance extends beyond monitoring the disease, encompassing the prediction of successful treatment outcomes following RRA (28, 33). Thyroglobulin (Tg) has a half-life of 1 – 3 days and is anticipated to reach its nadir within 3 – 4 weeks in patients who have undergone TT (6, 28). The levels of Tg post-TT influenced by various factors including

the presence of anti-Tg antibody (anti-TgAb), the residual amount of thyroid tissue, the presence of metastatic foci, the timing it was taken post-operatively and also the TSH level at the time of Tg measurement (34). Poor RRA outcome has been found with sTg of more than 5 ng/mL in DTC regardless of the I-131 activities given (28).

CECT is an important preoperative imaging modality usually requested by the primary surgeon for surgical planning strategy especially in large and locally invasive DTC (32). In preparation for a patient who is going to receive RAIT, it is necessary to inquire about the possibility of high-dose iodine exposure prior and ensure low-iodine diet for around 1 – 2 weeks beforehand as per ATA guidelines 2015 (6). This is to reduce the iodine pool inside patient's body prior to RAIT to maximise the efficacy effect of the administered activity. This will be more of a concern if the patient is given a high-dose iodine exposure for example the usage of iodinated contrast media in CT imaging pre-operative or post-operatively in staging of the disease of suspected distant metastasis (32) before RAIT. There are also reports in some literature that, a single iodinated contrast administration would likely perturb radioiodine uptake for as minimum as 3 months and may last as long as 2 years (35). In a study done by Sohn *et al*, a month delayed in radioiodine therapy for DTC did not have significant difference in treatment outcome as compared to those who was being delayed for therapy up to 6 months post-CECT (31).

Delayed RRA post-operatively in patients with DTC also had been found to be one of the contributing factors that may lead to poor outcome of the therapy (24, 36). In a retrospective study by Higashi *et al* of 198 patients in Kyoto University Hospital in 2009, it was found that delaying the RAIT for more than 180 days will increase the failure treatment outcome and also the risk of death by 4.22 times higher than those subjects who

were treated within 180 days (36). In another retrospective study by Li et al in 235 patients of low- to intermediate-risk DTC has suggested that delaying RRA by three months and more post-TT results in low rate of successful treatment outcome than those who are given RRA within three months post-operatively, 62.5% vs 78.1%. Apart from that, their study also showed that the rate of incomplete response (biochemical incomplete and structural incomplete response) was comparatively higher in those received RRA later than 3 months than within 3 months post-TT, 18.8% and 4.3% respectively (24). Having said that, the optimal timing for RRA and the risk of delayed RRA post-TT have not been in consensus in any of the available current guidelines. The time interval of RRA post-TT varied by country and many contribution factors such as facility availability, patient's socioeconomic status, and disease-related factors must be taken into consideration (37).

2.5 Conclusion

In conclusion, RRA in low-risk DTC is still debatable despite reported lower recurrence risk of only 1% - 6% in robust literatures. According to ATA guidelines 2015, roles of RRA in post-operative low-risk DTC is still practicable depending on the treating health care professional decisions after taking into consideration of patient's risk factors as well as patient preferences (6). The use of minimum I-131 radioactivity should be obtained in the selected patients subjected to remnant ablation to avoid unnecessary exposure to radiation (16). Interestingly, the successful rate of remnant ablation in DTC among the Asian populations are still suboptimal compared to the widely available literature reported from the west countries with 55.6% - 84.2% of successful rate (16 – 21). The primary tumour size, pre-ablation sTg value, pre-therapy CECT, and delayed RRA of more than 3 months post-TT have been reported as the culprit for poor treatment outcome of RRA in low-risk DTC.

3.0 RATIONALE / BENEFITS OF THE STUDY

In IKN, patients with low-risk DTC as per ATA guidelines 2015 will be given an option to receive RAIT or not. At present, there is no guidelines that clearly scrutinise the definite criteria for RRA when it comes to low-risk DTC. Although Estamib12 study has showed there is no difference in disease recurrence between the follow-up and treated patients with RRA in low-risk DTC, it is still worth mentioning that this study portrayed the treatment outcome in our local setting as the reported successful rate of RRA in low-risk DTC in several reported Asian's literatures are still sub-optimal. This study is also to identify the possible risk factors that may result in poor treatment outcome of RRA in low-risk DTC post-TT in our local setting. In continuum of it, individualized care plan can be provided by the treating Nuclear Medicine Physician to optimize the outcome following the therapy.

3.1 Aim

Determine the outcome of RRA in low-risk DTC in IKN and possibly identify the contributing co-factors that may result in poor treatment outcome.

3.2 Objectives

3.2.1 General Objective

- To determine the outcome of RRA in low-risk DTC in IKN.

3.2.2 Specific Objectives

- To ascertain the factor of primary tumour size in determining successful RRA of low-risk DTC according to tumour classification as per AJCC 8th edition (T1a, T1b, T2, T3a).
- To determine the value of pre-ablation sTg in predicting the treatment outcome.
- To scrutinise the effect of pre-therapy CECT in outcome of RRA in low-risk DTC.
- To assess the impact of delayed RRA in low-risk DTC post-TT in its treatment outcome.

3.3 Hypothesis Statements

- *Null hypothesis:* The outcomes of RRA in low-risk DTC would not be affected by the tumour size, pre-ablation sTg value, pre-therapy CECT, delayed RAIT post-TT in low-risk DTC patients.
- *Alternative hypothesis:* Large primary tumour size, high pre-ablation sTg value, had pre-ablation CECT and delayed RAIT post-TT in low-risk DTC will result in poor treatment outcome.

4.0 METHODOLOGY

4.1 Study Design, Study Location and Study Period

A retrospective study was carried out in Nuclear Medicine Department of Institut Kanser Negara (IKN), Malaysia, from the period of January 1, 2017, until December 31, 2020.

4.2 Study Sample

The data was retrieved retrospectively from the patient's registry system via "*Fisicien*" system. All new cases referred to Nuclear Medicine Department of IKN from January 1, 2017, until December 31, 2020, for RRA were reviewed.

Only patients of low-risk DTC that opted for RAIT were selected for the data collection. The samples were classified according to their tumour size according to the 8th edition AJCC cancer staging manual. All data including their pre-ablation sTg values, the time frame from the post-TT to the RRA as well as whether or not CECT has been performed prior to therapy were collected.

The images of the post-ablation and diagnostic I-131WBS scan were retrieved from the Philips BVX-CT dual head gamma camera database in Nuclear Medicine Department of IKN.

4.3 Sample Size Calculation

Objective 1: To determine the outcome of successful remnant ablation in DTC (Liu *et al.*, 2013.)

1 proportion – Estimation	
Proportion (p)	84.75 %
Precision	5 %
Significance level (α)	0.050
Drop-out	10 %
Sample size	199
Sample size (with drop-out)	222

Objective 2: To determine the association of affecting factors towards successful remnant ablation in DTC (Wang *et al.*, 2018 & Li *et al.*, 2018).

1 proportion - Estimation	
Proportion (p)	90.0%
Precision	5 %
Significance level (α)	0.050
Drop-out	10 %
Sample size	134
Sample size (with drop-out)	147

Objective 3: To determine the effect of pre-ablation CECT towards treatment outcome (Padovani *et al.*, 2012)

1 mean – Hypothesis Testing, $H_0 = 0$	
Standard deviation (σ)	9.150
Expected difference (Δ)	5.000
Significance level (α)	0.050
Power ($1-\beta$)	0.800
Drop-out	10%
Sample size	27
Sample size (with drop-out)	30

The sample size of this study was obtained using Sample Size Calculator software by Arifin, W. N. (2017). Sample size calculator (Version 2.0). A minimum number of 222 patients were collected from “*Ficisien*” with estimation of 10% drop-out.

4.4 Inclusion and Exclusion Criteria

4.4.1 Inclusion Criteria

- All new referred low-risk DTC patients opted for RAIT, with the intent for RRA in DTC.
- Underwent TT prior to therapy.
- DTC with no evidence of extra-thyroidal extension or distant metastasis at the time of presentation.
- Clinically no nodal metastasis or ≤ 5 pathological regional nodal (N1) micrometastases (< 0.2 cm in largest dimension).
- DTC which categorised as ATA low-risk during initial risk stratification upon presentation
- Low-risk DTC received I-131 ≤ 100 mCi for the RRA.

4.4.2 Exclusion Criteria

- Patients who had repeated RAIT.
- Patients who had previous external beam radiotherapy or other form of radiation therapy to the neck.
- Patients who had previously received chemotherapy for other malignancies.
- Patients who had radiological imaging or histological confirmed extra-thyroidal or distant metastasis.
- PTC with aggressive histological features such as tall cell, hobnail variant and columnar cell carcinoma.
- Patients who received I-131 activity of > 100 mCi which is a not a standard administered activity of I-131 in a low-risk DTC.

4.5 Criteria for Successful RRA

Patient needs to comply with all the criteria to be categorised as successful outcome of RRA which was assessed after patient had done the second diagnostic I-131 WBS. Interpretation was based on the images and report of post-ablation I-131 WBS and the two subsequent diagnostic I-131 WBS. Post-ablation WBS was performed 4 days after the administration of I-131 whereas the diagnostic I-131 WBS was performed 2 days after 5mCi of I-131 was given. The diagnostic WBS was scheduled at 6 months and 12 months post-RRA. Please refer to Appendix B for the conceptual framework.

Successful remnant ablation was defined as excellent response based on ATA guidelines 2015 in response-to-therapy assessment. Henceforth, an excellent response is defined as sTg <1 ng/mL in the absence of structural or functional evidence of disease as in two negative diagnostic I-131 WBS and in the absence of anti-thyroglobulin antibody (anti-TgAb). On the other hand, unsuccessful remnant ablation was defined as indeterminate, biochemical, or structural incomplete response. Please refer to Appendix C for the treatment response classification.

4.6 Data Collection

The collection of data was retrieved from local database by assessing the “*Ficisien*” software. The patient’s data such as the histopathological characteristic, date of diagnosis, date of post-TT, presence of pre-ablation CECT, date of RRA, activity of iodine-131 given, and biochemical parameters such as pre-ablation thyrotrophin (TSH), pre-ablation sTg as well as the anti-TgAb status were collected. The post-ablation and diagnostic I-131 WBS images were retrieved from Philips BVX-CT dual head gamma camera database in Nuclear Medicine Department, IKN.

All the patients’ data are kept confidential by the principal investigator. The data collection form for each of the included samples in this study were kept primarily by the principal investigator and only can be assessed by the third party after the agreement being made with the co-researchers to protect the patients’ confidentiality. All the data will be kept for 2 years after the completion of the study and will be disposed thereafter. The data presented as figures in the final study, and none of the patient’s personal information being revealed in the final writing. The “*Patient Information Sheet*” is available in Appendix D.

4.7 Data Analysis

The data analysis was performed using IBM SPSS Statistics 26 for Window Version 11.0. Descriptive statistics were presented as frequency, mean \pm standard deviation for normally distributed data, or median for skewed data. The comparison between two groups was conducted using the Chi-square test. For unpaired data, differences in distribution between groups were analysed using either independent t-test for normally distributed data or independent Mann-Whitney U-test for skewed data, depending on the distribution characteristics of the data. To identify independent affecting factors that may yield in non-successful treatment outcome of remnant ablation in low-risk DTC, multivariate logistic regression analysis was performed by adjusting the possible confounding factors. ROC curve analysis was generated for pre-ablation sTg levels. The cut-off values for sTg were chosen using intercept method to predict the successful RRA in low-risk DTC. A value of $p < 0.05$ is regarded as statistically significant.

4.8 Ethics and Disclosure

No personal data was obtained in this study. Each patient has an identity code to preserve confidentiality of the data, and this applies to all data collection sheets and analyses as well. All data was stored in a Universal Serial Bus (USB) flash drive with protected password and kept primarily by the principal investigator in a locked drawer. The data can only be assessed by the third party after the agreement being made with the co-researchers to protect the patients' confidentiality. All the data will be kept for 2 years after the completion of the study and will be disposed thereafter.

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 ID: NMRR-21-1359-60346; APPENDIX E). This study also has been approved by the Jawatankuasa Etika Penyelidikan Manusia (JEPeM) of Universiti Sains Malaysia (USM JEPeM ID: USM/JEPeM/21080556; APPENDIX F).

The author has no conflicts of interest to disclose, which may influence the impartiality of this study.

5.0 RESULTS

5.1 Demographic and Clinical Data

A total of 231 low-risk DTC patients were eligible to be recruited into the study from the data collected retrospectively from January 1, 2017, till December 31, 2020. However, only 212 patients were included in our analysis as 7 of the patients did not turn up for subsequent diagnostic I-131 WBS post-RRA and 12 of them were given activity of I-131 of more than 100mCi.

Out of 212 patients, 34 are males and 178 are females, aged 22 – 79 years with an average age of 41 years. Histopathologically, 181 patients were diagnosed with low-risk PTC and the remaining were low-risk FTC, the primary tumour size ranging from 0.1 cm to 8.5 cm with a mean of 3.0 cm with disease limited to the thyroid. 12 patients have central neck nodal micrometastases (level VI) on post-operative HPE report and all of them have less than 5 nodal micrometastatic disease. 203 of these patients were diagnosed with Stage I and the remaining 9 with Stage II of the disease. Out of the 212 patients, 48 of them had done CECT pre-RRA.

Patients received RRA ranges from 17 days up to 363 days post-TT with the median of 112 days. They were further categorised into 2 groups of time interval between post-TT and RRA): Group of intervals within 90 days or less (n = 65), and group of intervals of more than 90 days (n = 147). The cut-off points 90 days of time interval between post-TT and RRA were adapted from studies by Li *et al* 2018 and Ahn *et al* 2020 (24, 37).

124 patients received I-131 activity of ≤ 80 mCi. This included 1 patient received 30 mCi and another one who received 50 mCi of I-131. The remaining 88 patients were given 100 mCi. Out of 212 patients, 15 of them had non-stimulated TSH of less than 30 mIU/L with the remaining were all stimulated with value of ≥ 30 mIU/L.

In adherence to our local setting prior to RAIT, all the subjected patients were advised to withhold Levothyroxine consumptions for 1 month and to be on low-iodine diet (LID) for 2 weeks for the preparation prior to the therapy. Routine blood investigations such as their thyroid function test and serum Tg were taken in the morning prior to administration of I-131 in the afternoon on the same day.