PROGRESSION-FREE SURVIVAL AND 5-YEAR CLINICAL OUTCOMES POST EMPIRICAL HIGH DOSE IODINE-131 (I-131) THERAPY IN TENIS SYNDROME AND MIXED DISEASE OF DIFFERENTIATED THYROID CARCINOMA

BY

DR. WAN MUHD ANAS BIN WAN HUSSAIN

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DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Master of Medicine in Nuclear Medicine. It is also not to be sent to other universities. With that, this research might be used for consultation and will be photocopied for reference.

Dr. Wan Muhd Anas bin Wan Hussain

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ABBREVIATIONS

AJCC	American Joint Committee on Cancer
CT	Computed Tomography
DTC	Differentiated Thyroid Carcinoma
EBRT	External Beam Radiotherapy
F-18 FDG	Flourine-18 Flourodeoxyglucose
FTC	Follicular Thyroid Carcinoma
HKL	Hospital Kuala Lumpur
I-131	Radioactive Iodine-131
I-131 WBS	Iodine-131 Whole Body Scan
MRI	Magnetic Resonance Imaging
PET-CT	Positron Emission Tomography – Computed Tomography
PTC	Papillary Thyroid Carcinoma
RAI-131	Radioactive Iodine-131
RR-DTC	Radioiodine Refractory Differentiated Thyroid Carcinoma
Serum anti-Tg	Serum anti-Thyroglobulin antibody
Serum Tg	Serum Thyroglobulin
SUVmax	Standardize Uptake Value Maximum
T4	Thyroxine Hormone
TENIS	Thyroglobulin Elevated Negative I-131 Scan
TFT	Thyroid Function Test
TKI	Tyrosine Kinase Inhibitor
TSH	Thyroid Stimulating Hormone
UICC	Union for International Cancer Control

ABSTRAK

Latar belakang: Pesakit kanser tiroid yang telah refraktori atau tidak bertindak balas dengan baik terhadap rawatan ablasi radioaktif iodin (*Iodine-131*, I-131) mempunyai prognosis yang lemah disebabkan oleh pilihan rawatan yang sangat terhad. Keterbatasan ubat *tyrosine kinase inhibitor* (TKI) dan sifat kanser tiroid yang secara amnya kurang agresif membuatkan pakar klinikal lebih cendurung untuk merawat pesakit ini secara empirik dengan dos tinggi rawatan ablasi radioaktif iodin (I-131).

Metodologi: Kajian kohort secara retrospektif ini menentukan jangka hayat tanpa kemerosotan penyakit, *progression-free survival* (PFS) pesakit yang telah menghidapi kanser tiriod dengan TENIS sindrom atau *mixed iodine-avid and non-iodine avid disease (mixed disease)* yang telah menjalani pembedahan tirodektomi dan rawatan radioaktif iodin. Kohort A adalah pesakit kanser tiroid yang telah diberi rawatan dose tinggi I-131 secara empirik manakala kohort B adalah pesakit yang telah didiagnos dengan kondisi yang sama tetapi tidak diberikan rawatan radioaktif iodin dos tinggi secara empirik. Semua pesakit di kohort A dan B telah dipantau untuk lima tahun bagi menentukan respon klinikal terhadap rawatan yang diberikan.

Keputusan: Daripada 63 pesakit, 46 pesakit (73%) adalah pesakit *TENIS syndrome* manakala 17 pesakit dikenalpasti sebagai *mixed disease*. Terdapat 40 pesakit (63.5%) dalam kohort A, yang terdiri daripada 27 pesakit *TENIS syndrome* dan 13 pesakit *mixed disease*. Kohort B diwakili sebanyak 23 pesakit yang mana terdiri daripada 19 pesakit *TENIS syndrome* dan 4 pesakit *mixed disease*. Terapi empirik radioaktif iodin (I-131) telah menunjukkan PFS yang lebih panjang berbanding kumpulan kawalan (hazard ratio 0.603; 95% CI, 0.308-1.179; p = 0.139) dengan 40% pengurangan risiko

untuk penyakit bertambah teruk (*disease progression*) dalam masa 5 tahun kajian. Median PFS untuk kohort A adalah 4.7 tahun manakala kohort B adalah 3.6 tahun. Walaubagaimanapun, kajian ini tidak menunjukkan statistik yang signifikan. Pada tahun kelima selepas diagnosis, 20% (n=8/40) pesakit kohort A menunjukkan *excellent response* terhadap rawatan berbanding 26% (n=6/23) pesakit dari kohort B. Walaubagaimanapun, majoriti pesakit (80% untuk kohort A dan 83% dari kohort B) masih menunjukkan respon yang tidak penuh secara biokimia dan secara fizikal.

Kesimpulan: Rawatan empirik dos tinggi radioaktif iodin I-131 memanjangkan jangka hayat tanpa kemerosotan penyakit (PFS) untuk pesakit kanser tiroid yang didiagnos sebagai *TENIS syndrome* atau *mixed disease*. Kajian ini menunjukkan rawatan empirik dos tinggi radioaktif iodin I-131 boleh diberi untuk mengelakkan kemorosotan penyakit walaupun tidak signifikan secara statistik.

ABSTRACT

Title: Progression-free survival and 5-year clinical outcomes post empirical high dose Iodine-131 (I-131) therapy in TENIS syndrome and mixed disease of differentiated thyroid carcinoma.

Background: Patients with radioactive Iodine-131 (I-131) – refractory differentiated thyroid carcinoma have a poor prognosis due to limited treatment options. The limited availability and expensive tyrosine kinase inhibitor and indolent behavior of differentiated thyroid cancer are the factors that drive clinicians to treat these patients empirically with high dose I-131 therapy for curative and disease control intent.

Method: A retrospective cohort study of progression-free survival in patients who developed TENIS syndrome and mixed disease of differentiated thyroid carcinoma post total thyroidectomy and remnant ablation from 2010-2018. Cohort A included treatment group in which empirical high dose I-131 therapy was administered, and cohort B were those diagnosed with similar conditions but not given therapy. All patients in both cohorts were followed up for five years to look for clinical outcomes in response to treatment.

Findings: Sixty-three patients were included, 46 (73%) patients developed TENIS Syndrome and 17 (27%) patients were identified as mixed disease. There were 40 patients (63.5%) who received the empirical high dose I-131 were allocated to cohort A and 23 patients (36.5%) who did not receive empirical high dose I-131 were assigned to the controlled group (cohort B). Twenty-seven patients with TENIS syndrome and 13 patients with the mixed disease were treated with empirical high

dose I-131 therapy (cohort A). Empirical high dose I-131 therapy showed prolonged progression-free survival (PFS) compared to the controlled group (hazard ratio, 0.603; 95% CI, 0.308-1.179; p = 0.139) with a 40% reduction in the risk of disease progression at any given time over five years with median PFS in cohort A is at 4.7 years while cohort B is 3.6 years, though it is not statistically significant. At five years, only 20% (n=8/40) of patients in the treatment group had excellent response compared to 26% (n=6/23) in the surveillance group. However, 80% (n= 32/40; cohort A) and 83% (10/12; cohort B) remained structurally and biochemically incomplete response to therapy.

Conclusion: Empirical high dose I-131 therapy prolongs progression-free survival in patients with TENIS syndrome and mixed disease. These results suggest that empirical high dose I-131 therapy represents a treatment option for these patients to prevent further disease deterioration despite statistically does not show significant results.

INTRODUCTION

1. INTRODUCTION

Thyroid carcinoma, the most prevalent type of endocrine malignancy, has been getting more common over the past three decades in the United States according to Surveillance, Epidemiology and End Results Program (SEER)-based study. The rise of the incidence of thyroid cancer make it the eighth most common newly diagnosed cancer overall and the fifth commonest new malignancy diagnosed in women in the USA (Olson et al., 2019). Recent worldwide Global Cancer Statistics 2020: GLOBOCAN Estimates of Incident and Mortality showed that thyroid cancer accounted for 586000 cases worldwide and placed in 9th place for incidence in the year 2020. The global incidence rate is three times more common in females than in males, according to age-standardized incidence rate, ASR (Sung et al., 2021).

Differentiated thyroid cancer (DTC) is a type of thyroid cancer that arises from thyroid follicular cells and accounts for over 90% of all thyroid malignancies (Xing et al., 2013). The most prevalent type of DTC is papillary thyroid carcinoma (PTC), followed by follicular thyroid carcinoma (FTC), Hürthle cell carcinoma, and poorly differentiated thyroid carcinoma (PDTC).

Treatment with surgery, followed by radioactive iodine (RAI) ablation and TSH suppressive therapy result in a five-year overall survival rate of 97.7% for the majority of thyroid cancer patients (Riesco-Eizaguirre et al., 2016). The radioactive Iodine-131 (I-131) therapy for remnant ablation following thyroidectomy has been proven to reduce disease recurrence and extend survival in high-risk differentiated thyroid carcinoma patients and it is considered as the standard of treatment for these patients (Carballo and Quiros, 2012). Nonetheless, 20% of patients might develop

locoregional recurrence while 10% may present with distant metastases within ten years (Gallardo et al., 2020).

Radioactive Iodine-131 refractory differentiated thyroid cancer (RR-DTC) occurs in around one-third of patients with structural evidence of locoregional or metastatic disease. RR-DTC loses the ability for iodine uptake causing ineffective radiation doses delivered to the cancer cells thus unable to treat the metastatic lesions (Mu et al., 2019). Therefore, the behaviour of the malignant cells defines the RR-DTC than its specific histopathology. Patients diagnosed with RR-DTC have a grim survival rate at 5-year reduced to 19% (Durante et al., 2006).

Therefore, this study aims to assess the demographic, pre-treatment histopathological characteristic and clinical features such as risk assessment of DTC that progress to RR-DTC, particularly in patients with TENIS syndrome that showed elevated thyroglobulin level with negative findings on I-131 whole body imaging and in patients with mixed iodine-avid and non-iodine avid disease of differentiated thyroid carcinoma. This study will retrospectively evaluate the efficacy of empirical high dose I-131 therapy in terms of progression-free survival and clinical outcomes (post-therapy response) in patients with TENIS syndrome and mixed disease of DTC. Exploratory analyses were conducted to identify potential predictive and prognostic biomarkers.

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 EPIDEMIOLOGY OF THYROID CANCER

In Malaysia, thyroid cancer is now the third most prevalent new cancer diagnosis and the ninth most common disease among women. Nevertheless, thyroid cancer is currently in the 18th place in Malaysia for new cancer diagnoses (MNCRR, 2019).

Despite not-so-well understood aetiology of thyroid carcinoma, the risk factors for thyroid cancers have been established. Previous exposure to ionising radiation exposure during childhood and familial thyroid carcinoma carry an increase of 10-fold of the risk (Pal et al., 2001). Other factors that have been associated with higher risk of thyroid cancer include overweight, chronic hepatitis, hormonal exposures, and specific occupational and environmental exposures (Sung et al., 2021).

The most frequent initial manifestation of thyroid cancer is a painless palpable nodule in the neck. The malignant features of neck nodules are usually hard and fixed to the thyroid gland that may gradually increase in size. The more aggressive type will have rapid growth of the nodules associated with voice hoarseness and cervical lymphadenopathy. Aggressive cancer may also manifest as late-stage with bone or lung metastases in which further evaluations suggest the primary thyroid pathology (Nguyen et al., 2015).

Over 90% of all thyroid malignancies are histologically attributed to differentiated thyroid cancer (DTC), a subtype of thyroid cancer that develops from thyroid follicular cells. Papillary thyroid carcinoma (PTC) is the most prevalent type of differentiated thyroid carcinoma. Histopathologically, it is a malignant epithelial

tumour of thyroid follicular cells with evidence of follicular differentiation and series of specific nuclear features. Follicular thyroid carcinoma (FTC) is a malignant tumour that lacks the nuclear features of papillary thyroid carcinoma. (Fugazzola and Fuhrer, 2019).

2.2 DIAGNOSTIC EVALUATION OF THYROID CANCER

Clinical history taking, physical examination, biochemical evaluation, fine-needle aspiration cytology (FNAC) and ultrasound examination are the mainstays in evaluating thyroid nodules to differentiate malignant from benign disease.

2.2.1 Pre-Operative Imaging Modalities

Readily available computed tomography (CT) imaging for various indications increases the incidental findings of thyroid nodules. The emergence of molecular imaging with positron emission tomography particularly Flourine-18 FDG PET/CT further increases incidental detection of hypermetabolic nodules. Sonographic evaluation with neck ultrasound (US) is recommended for patients with suspicious thyroid nodules. Ultrasound evaluates sonographic features of thyroid nodules and the presence of suspicious cervical lymphadenopathy (Shimamoto et al., 1998). TIRADS scoring is used in the evaluation of sonographic features of thyroid nodules and guides fine-needle aspiration procedure for cytological assessment (Srinivas et al., 2016).

Other pre-operative imaging modalities are required in clinically advanced local disease to look for extrathyroidal disease extension to the strap muscles or major neck structures such as trachea, oesophagus, larynx, or vessels. Computed tomography

(CT) is usually acquired preoperatively in the event of suspected locoregional and distant metastases.

2.2.2 Fine Needle Aspiration Cytology (FNAC)

Bethesda System for Reporting Thyroid Cytopathology gives FNAC as the most cost-effective and accurate preoperative method for thyroid nodule evaluation. It also gives an estimation of malignancy risk for each of six diagnostic categories. It has proven to be a robust and effective classification scheme to guide clinicians in the management of thyroid nodules (Bongiovanni et al., 2012).

Table 2.2.2.1 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic category	**Cytological diagnosis**	**Risk of Malignancy, %**
I	Non-diagnostic or unsatisfactory	1-4
II	Benign	0-3
III	AUS/FLUS	5-15
IV	FN/SFN	15-30
V	Suspicious of malignancy	60-75
VI	Malignant	97-99

AUS: Atypia of undetermined significance; FLUS: Follicular lesion of undertermined signicance; FN: Follicular neoplasm; SFN: Suspicious of follicular neoplasm

2.3 INITIAL THERAPY FOR DIFFERENTIATED THYROID CARCINOMA

The goals of initial therapy include increasing overall and disease-specific survival, minimising persistent or recurrent disease occurrence, and permitting correct staging and dynamic risk stratification of the disease while minimising unwanted therapy-induced morbidity and unnecessary treatment (Haugen et al., 2016). Surgery with unilateral or total thyroidectomy is the mainstay treatment option for differentiated thyroid carcinoma. However, the operative approach of thyroidectomy depends upon the primary tumour and the presence of extrathyroidal extension or lymph node involvement (Yip et al., 2011).

2.4 STAGING AND RISK STRATIFICATION

Postoperative staging provides prognostic information for treatment approach and surveillance. It enables better understanding among treating clinicians regarding patients' descriptions on risk-stratification as well as for the research purposes. The latest 8th edition of AJCC/UICC TNM classification and staging (Figure 2.4.1 and 2.4.2) is recommended according to its applicability in disease-specific mortality prediction and cancer registries purposes (Tuttle et al., 2017).

The 2009 ATA Initial Risk Stratification System (Figure 2.4.3 and 2.4.4) are used for DTC patients post-thyroidectomy. This risk-stratification system is a clinically practical and accurate method for predicting the likelihood of persistent disease or future recurrences. A three-tiered system of the ATA initial risk stratification method classifies DTC patients as having a low, intermediate, or high

risk of recurrence or persistent disease according to its post-operative clinicopathologic data (Cooper et al., 2009). However, the risk of disease recurrence, disease-specific morbidity and death might alter over time due to the dynamic nature of the disease and its response to therapy. Therefore, the initial risk assessment for possible recurrences should be periodically adjusted during follow-up.

TNM definitions (AJCC 8e)

for papillary, follicular, poorly differentiated, Hürthle cell, medullary, and anaplastic thyroid carcinomas

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3*	Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles
T3a*	Tumor > 4 cm limited to the thyroid
T3b*	Gross extrathyroidal extension invading only strap muscles (sternohyoid) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
NX	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph nodes metastasis
N0a*	One or more cytologic or histologically confirmed benign lymph node
N0b*	No radiologic or clinical evidence of locoregional lymph node metastasis
N1*	Metastasis to regional nodes
N1a*	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1b*	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
M0	No distant metastasis
M1	Distant metastasis

* all categories may be subdivided as solitary tumor (s) and multifocal tumor (m) – the largest tumor determines the classification

Figure 2.4.1 AJCC 8th Edition TNM Classification System for Differentiated Thyroid Carcinoma. Courtesy of Bychkov A. AJCC/TNM Staging. PathologyOutlines.com website.

Staging flowchart for differentiated thyroid cancer (AJCC 8e)

Age at diagnosis	M category	Gross ETE	Structures involved	Tumor size	N category	Stage
<55 years	M0	yes or no		any	any	I
	M1	yes or no		any	any	II
≥ 55 years	M0	no		≤ 4 cm (T1-2)	N0/Nx	I
					N1a/N1b	II
				> 4 cm (T3a)	any	II
		yes	only strap muscle (T3b)	any	any	II
			s/cutaneous, larynx, trachea, esophagus, RL nerve (T4a)	any	any	III
			prevertebral fascia, encasing major vessels (T4b)	any	any	IVA
	M1	yes or no	any or none	any	any	IVB

Figure 2.4.2 AJCC 8th Edition TNM Staging System for Differentiated Thyroid Carcinoma. Courtesy of Bychkov A. AJCC/TNM Staging. PathologyOutlines.com website.

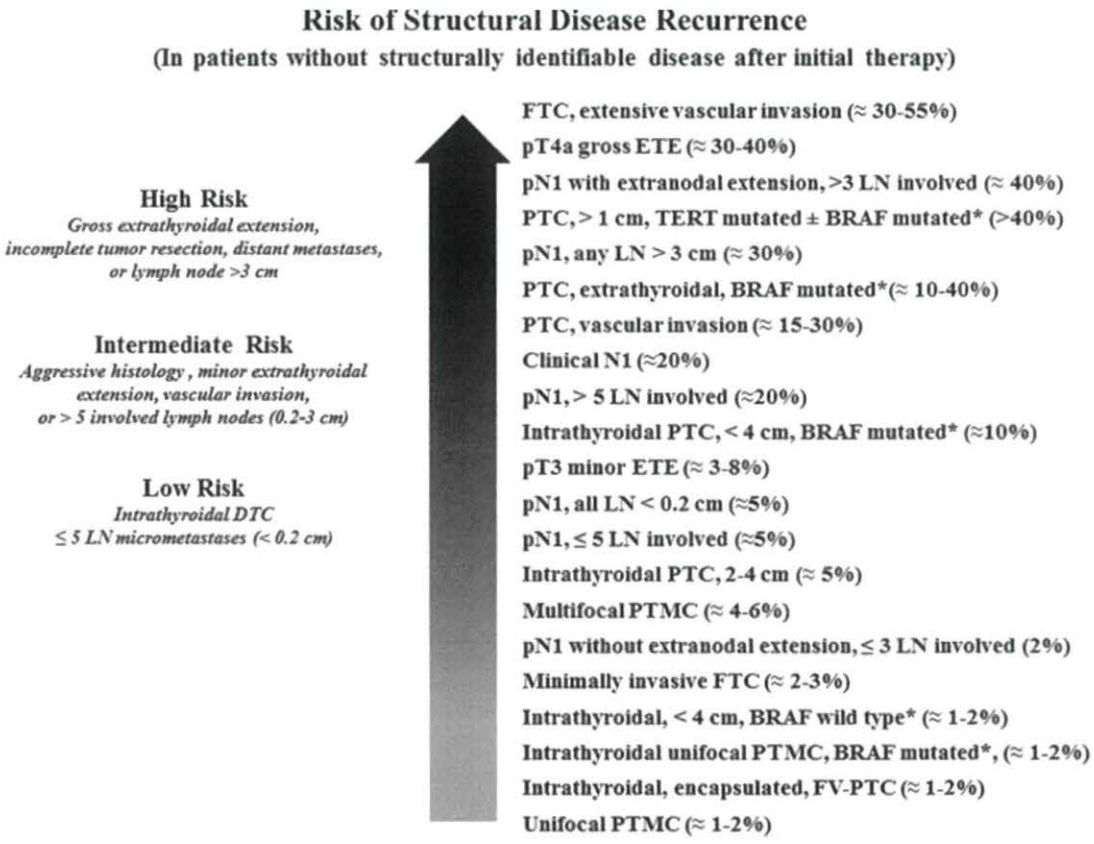

Figure 2.4.3 Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy. Adapted from Modified Initial Risk Stratification System (Haugen et al., 2016).

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

Figure 2.4.4 ATA 2009 Risk Stratification System with Proposed Modifications (Haugen et al., 2016)

2.5 RADIOACTIVE IODINE (I-131) THERAPY

Radioactive iodine (RAI) I-131 has been utilised since the 1940s for the treatment of differentiated thyroid carcinoma. Thyroid tissue has the ability to take up iodine from the blood. Similar mechanism allows radioiodine to be trapped and concentrated in thyroid follicular cells due to presence of membrane sodium-iodide transporter (Spitzweg et al., 2001). The theranostic property of Iodine-131 (I-131) causes acute thyroid cell death by emission of beta particles while emission of gamma radiation that permits diagnostic evaluation of the treatment (Choudhury et al., 2018).

Radioiodine is orally administered for thyroid remnant ablation post thyroidectomy, or as adjuvant therapy to eradicate potential micro-metastases, residual or persistent malignant tumours. I-131 whole-body scan (WBS) is also used for diagnostic purposes for localisation and tissue uptake prior to ablation therapy. The radioactive Iodine-131 (I-131) therapy following thyroidectomy for remnant ablation and adjuvant therapy has been shown to reduce rates of recurrence and extend survival in high-risk papillary thyroid cancer patients and it is considered the standard of treatment for these patients (Carballo and Quiros, 2012). However, radioiodine efficacy treatment may be affected by inadequate patient preparation, characteristics of the tumour, site of metastases and the activity of I-131 administered (Carballo and Quiros, 2012).

2.6 RADIOIODINE REFRACTORY DIFFERENTIATED THYROID CARCINOMA

Radioactive Iodine-131 refractory differentiated thyroid cancer (RR-DTC) occurs in approximately one-third of DTC patients with structural evidence of locoregional or metastatic disease. RR-DTC loses the ability for iodine uptake causing ineffective radiation doses delivered to the cancer cells thus unable to treat the metastatic lesions (Mu et al., 2019). Therefore, the behaviour of the malignant cells defines the RR-DTC than its specific histopathology. Durante et al., found that patients diagnosed with RR-DTC have a grim survival rate at 5-year reduced to 19% (Durante et al., 2006). Other related studies found that patients with RR-DTC metastatic disease have less than 50% overall survival at three years (Riesco-Eizaguirre et al., 2016).

The classification of radioiodine-refractory DTC (RR-DTC) as follows (Haugen et al., 2016):

1. The malignant or metastatic tissue does not ever concentrate RAI (no uptake outside the thyroid bed at the first therapeutic WBS)
2. The tumour tissue loses the ability to concentrate I-131 after previous evidence of RAI-avid disease (TENIS syndrome and Dedifferentiated Thyroid Carcinoma)
3. I-131 uptake in some lesions but not in others (mixed disease)
4. The progressive metastatic disease progresses despite significant concentration of I-131.

Identifying radioiodine-refractory differentiated thyroid carcinoma requires imaging modalities such as I-131 WBS, F-18 FDG PET/CT and conventional radiological

imaging. As mentioned earlier, I-131 whole body scan (WBS) is used to localise to the functioning thyroid tissue remnant and residual or recurrent iodine-avid disease with high accuracy of I-131 WBS (up to 90%) and high specificity (91%-100%). However, it has a relatively low sensitivity (27-55%) (Mu et al., 2019).

As the disease progresses with dedifferentiation, the malignant lesions lose their ability to uptake and concentrate radioiodine. Dedifferentiated thyroid carcinoma is diagnosed only during the course of the disease as it is not a histopathological entity. There is no available WHO classification to precisely define the pathological criteria of dedifferentiation. However, histopathological signs of dedifferentiation may be observed in the nuclei features, type of growth pattern, presence of high mitotic activity, and tissue necrosis in the malignant lesions (Fugazzola and Fuhrer, 2019).

In such events, the metabolic imaging of F-18 FDG PET/CT plays an essential role in the management of radioiodine refractory DTC (RR-DTC). This functional radiotracer combined with anatomical imaging allows locoregional or metastatic foci detection, evaluation of treatment efficacy and determination of prognosis prediction. Feine et al. (1995) reported an inverse association between I-131 and FDG absorption in thyroid cancer was assumed to be attributable to the loss of ability to concentrate I-131 during dedifferentiation, as well as an increased demand for glucose by tumour cells. (Mazzaferri, 2005).

TENIS syndrome is defined as elevated serum thyroglobulin with a negative I-131 WBS. The syndrome has been associated with several possible aetiologies; low activity of radioiodine I-131 administered (2-10 mCi) for the diagnostic whole body scan, "stunning" of radioiodine I-131 uptake by functional thyroid tissue, absence of immunoreactive cytoplasmic thyroglobulin and thyroxine of cancer tissue, small

volume tumour below gamma camera resolution, and mutation of sodium-iodine symporter expression causing dedifferentiation of the carcinoma with loss of function of the NIS to accumulate iodine (Onimode et al., 2013). On the other hand, the exogenous iodine ingestion or inadequate preparation prior to I-131 therapy causes blocking of RAI uptake in the cancer tissues, thus may also exhibit TENIS syndrome features.

Jung-Min Koh et al., through his article, evaluated the effects of therapeutic high dose Iodine-131 in the TENIS syndrome (Koh et al., 2003). The study found that administering an empirical high dose of Iodine-131 has a therapeutic effect observed for short-term palliation, when using serum Thyroglobulin as an index of tumour burden. It also revealed previously undiagnosed lesions in some patients.

Saima Riaz and colleagues concluded that empiric I-131 therapy plays a role in treating 'TENIS' syndrome as reflected by regression in thyroglobulin levels. Edward B. Silberstein found an empirical dose of 2775 MBq to 11100 MBq of I-131 given to patients with TENIS syndrome benefited 57% of patients who had scans that showed functioning thyroid tissue post-treatment on their whole-body scan (Silberstein, 2011). Ma et al. (Ma et al., 2009) and Mazzaferri et al. (Mazzaferri, 2005) justified the use of empirical high dose I-131 therapy when the thyroglobulin level exceeds10 ng/mL.

On the other hand, another group of radioiodine refractory illness is the mixed disease of differentiated thyroid carcinoma. The mixed disease shows a mixed disease of malignant tissue uptake; some lesions take up I-131 or FDG and some show concurrent tracer uptakes. However, the literature evaluating the effectiveness of radioiodine therapy in the group of RR-DTC has been scarce with insufficient

evidence to favour or reject the therapy. Nonetheless, no studies have demonstrated that continuing I-131 treatment is harmful.

However, ATA Guideline 2015 recommended that there is no role of further I-131 therapy in those patients with radioiodine refractory illness. However, there is no evidence from any randomised or prospective controlled trials to support or against I-131 treatment for DTC with TENIS syndrome or mixed disease to date. Nonetheless, the wider nuclear medicine community has expressed dissatisfaction with certain of the ATA Guideline 2015's recommendations on the diagnostic and therapeutic use of radioactive iodine-131. A consensus on the I-131 therapy was met from a joint statement by European Thyroid Association (ETA), the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and from the ATA (Michael Tuttle et al., 2019).

The Martiniques principles summarised the major point of discussion during first the meeting. One of the main principles was to clarify the definition and classification of the radioactive iodine I-131 refractory thyroid cancer (RR-DTC). Currently, the groups use the "clinical scenarios" to explain and discuss about the typical clinical features that raise the risk of developing refractory thyroid cancer in the presence of persistent or recurrent biochemical and structural evidence of the disease. The consensus concluded that a multidisciplinary approach tailored for individualised treatment for each patient taking into account the possible confounding factors and weighing the risk and benefits of further I-131 therapy.

JUSTIFICATION AND BENEFIT

3. JUSTIFICATION AND BENEFIT

3.1 PROBLEM STATEMENT

Currently, there is a lack of national registries for thyroid cancer patients in Malaysia. The latest Malaysia National Cancer Registry Report (MNCR) 2012-2016 does not specifically elaborate on the incidence of thyroid cancer as it is not in the ten selected cancer sites for further commentary (MNCRR, 2019). This makes it challenging to estimate new cases per year and the percentage of patients who become radioiodine refractory to I-131 therapy. Furthermore, no similar study had been done in the local and regional settings.

Empirical high dose I-131 has been practised in many local nuclear medicine centres, including our institution, mainly for those with TENIS syndrome and mixed iodine-avid and non-iodine avid diseases. In our institution, the maximum activity allowed of I-131 per patient is currently at 150 mCi (5550 MBq) as per permission by the local regulatory authority *Bahagian Kawalselia Radiasi Perubatan*, Ministry of Health. Therefore, all of our patients who had been subjected to empirical high dose I-131 therapy for the TENIS syndrome and mixed disease received 150 mCi (5550 MBq) of I-131 activity. Currently, the local Malaysian Consensus Guideline on Well-differentiated Thyroid Cancer on the standard practice in the management of thyroid disease has similar recommendations according to ATA Guidelines 2015.

The conflicting literature reviews on the role of Iodine I-131 therapy in the radioiodine refractory illness may give different opinions and school of thought in how to tackle these groups of patients. Thus, it delays the therapy or causing exhaustion of treatment option which can deteriorate the condition further.

We believe there is a significant role for the I-131 therapy to slow down the progression of the disease and prolong the survival rate among refractory DTC patients. Apart from that, the issue of financial constraint and availability and selection of patients for the expensive oral tyrosine kinase inhibitor treatment as our centre further emphasises the need for the empirical I-131 therapy.

Therefore, this study aims to assess the demographic, biochemical and pathological features, pre-treatment risk assessment of DTC that progress to TENIS syndrome and mixed disease (iodine-avid and non-iodine avid) of differentiated thyroid carcinoma. This study will retrospectively evaluate the efficacy of empirical high dose I-131 therapy in terms of progression-free survival and clinical outcomes post-therapy in patients with TENIS syndrome and mixed disease of DTC. These are to assess the role of I-131 in TENIS syndrome and the mixed disease (iodine-avid and non-iodine avid) of differentiated thyroid carcinoma.

3.2 BENEFIT OF THE STUDY

As there are conflicting literature reviews on the role of Iodine I-131 therapy in radioiodine refractory illness, this observational retrospective cohort study aims to determine the prognostic factors and survival outcomes in patients who have been treated with the empirical high dose of I-131 therapy in our centre.

Therefore, this study will increase the precision of the predicted treatment effect and identify the important prognostic factors attributed to refractory illness among differentiated thyroid carcinoma patients. This will allow early holistic intervention for those in the high-risk groups. The result of this study would be helpful

for the management of refractory thyroid carcinoma in our local clinical setting that has limited financial freedom.

Hopefully, this study would contribute to Principle 9 of Martinique Principles in filling up the gaps in information and data about the best indication of I-131 therapy in radioiodine refractory thyroid cancer. The ninth principle addressed significant gaps in our understanding and the body of evidence surrounding the most effective application of I-131 therapy. These gaps should be filled through appropriately planned prospective studies, randomised controlled trials, and patient-relevant outcome measures (such as quality of life, recurrence rate, progression-free, disease-specific, and/or overall survival).

OBJECTIVES

4. OBJECTIVES

4.1 GENERAL OBJECTIVE

This study aims to assess progression-free survival (PFS) and the role of empirical high dose of I-131 therapy in TENIS syndrome and mixed disease (iodine-avid and non-iodine avid) of differentiated thyroid carcinoma.

4.2 SPECIFIC OBJECTIVES

1. To evaluate progression-free survival post empirical high dose in patients with TENIS syndrome and mixed disease (iodine-avid and non-iodine avid) of differentiated thyroid carcinoma.
2. To identify demographic distribution, biochemical and histopathological features, risk stratification of TENIS syndrome and mixed disease (iodine-avid and non-iodine avid) of differentiated thyroid carcinoma
3. To evaluate clinical response to therapy following empirical high dose I-131 therapy in TENIS syndrome and mixed disease of differentiated thyroid carcinoma at five years of follow-up.

4.3 RESEARCH HYPOTHESIS

4.3.1 Null Hypothesis

Empirical high dose I-131 therapy does not significantly improve progression-free survival in patients with TENIS syndrome or mixed disease of differentiated thyroid carcinoma.

4.3.2 Alternative Hypothesis

Empirical high dose I-131 therapy has significant efficacy to improve clinical outcomes and progression-free survival in the treatment of TENIS syndrome and mixed disease (iodine-avid and non-iodine avid) of differentiated thyroid carcinoma.