ORIGINAL ARTICLE

Clinicopathological features and treatment outcome of paediatric differentiated thyroid cancer treated with Radioactive Iodine-131 therapy in Hospital Kuala Lumpur, Malaysia

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ABSTRACT

Background: Radioactive iodine ^{131}I (RAI) therapy is one of the definitive treatments for paediatric differentiated thyroid cancer (DTC) initiated at nuclear medicine departments. In Malaysia, there is a need to identify the standardisation of treatment regimes to align with international standards. We aimed to evaluate the clinicopathological features and the patient response to RAI therapy among paediatric DTC cases at Hospital Kuala Lumpur (HKL), Malaysia.

Methods: A retrospective, longitudinal study was conducted among paediatric DTC patients treated with RAI in HKL and followed up between 2000-2016. Sixty-five patients were studied (mean period: 58.8±36 months). The clinicopathological data of the patients was recorded, and descriptive analysis was made. The association between categorical and continuous data with disease status was assessed using chi-square and Kruskal-Wallis tests, p-value <0.05 taken as statistically significant.

Results: Most patients were female (78.5%), and adolescents comprised 89.2%. Pre-pubertal age, those presenting with cervical nodal involvement, extra-thyroidal extension and lymphovascular invasion were significantly associated with distant metastases at presentation. There was no mortality reported during the follow-up period. Sixty per cent of patients achieved remission, while 40% had persistent disease. The persistent disease was significantly correlated with distant metastasis at presentation (p=0.025).

Conclusions: Paediatric DTC manifests with a more extensive disease burden at presentation and requires multiple RAI doses. Despite this, it carries an excellent overall prognosis.

KEYWORDS:
Differentiated thyroid carcinoma, paediatric thyroid cancer, radioactive iodine, radionuclide therapy, treatment outcome

INTRODUCTION

Well-differentiated thyroid carcinoma (DTC) is a follicular cells-derived type of cancer that is iodine-avid and sensitive to thyroid-stimulating hormone (TSH). DTC in the paediatric population is rare, accounting for approximately 1.4% of all paediatric malignancies.[1] DTC has been reported as the 8th most common cancer in adolescents aged 15 – 19 years old and the second most common cancer among young females.[2] Compared to adults, paediatric DTC is more aggressive and has a higher risk of recurrence.[3] Nevertheless, this condition has an excellent long-term prognosis, having 30-year survival rates of 90–99%.[4] Treatment generally involves surgery, i.e. total thyroidectomy (TT), post-operative TSH suppression, and radioactive iodine ^{131}I (RAI) therapy.[5] Performing central compartment neck dissection (CND) based on an extensive *en-bloc* resection of lymph nodes by a high-volume thyroid surgeon is ideal for reducing the risk of recurrence, compared to the previously practised selective 'berry picking' approach.[6] In fact, between 38-45% of patients who undergo prophylactic CND are detected with microscopic metastasis, which can alter the risk stratification and management plan of these patients.[5]

Proper risk stratification is the basis for classifying patients into the appropriate treatment regime and follow-up programme. The classification of patients is made based on the risk of having persistent or metastatic disease. Based on the histopathological examination (HPE) of the operated specimens, the patients who have disease limited to the thyroid gland, with or without the presence of micro-metastasis to a small number of central neck nodes, are considered low risk.[7,8] Intermediate risk patients have extensive central neck lymph node involvement or minimal lateral neck lymph node involvement.[7] Based on the American Thyroid Association (ATA) 2015 guidelines, high-risk paediatric patients comprise of those with extensive regional disease or locally invasive disease, i.e., tumours with extrathyroidal extension (ETE) such as extra-capsular/ prevertebral fascia invasion; carotid artery/mediastinal vessels encasement; irrespective of whether or not they have distant metastasis.[9]

In the nuclear medicine departments that receive referrals for administering RAI therapy in Malaysia, dynamic risk stratification is performed by utilizing a ^{131}I whole-body scan (WBS), which is performed after the radioactive ablation is

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administered. The dynamic risk stratification is also aided by monitoring serial serum thyroglobulin (Tg) during follow-up clinic visits. Traditionally, RAI is administered as an adjuvant therapy, i.e. radioiodine remnant ablation (RRA), to destroy any residual thyroid tissue in the thyroid bed following TT. RRA enables post-ablation Tg estimations to be a good biomarker for the detection of early biochemical recurrence.[8] By monitoring post-RRA and post-RAI Tg levels, a dynamic risk assessment can be performed to detect the potential development of locoregional recurrence or the occurrence of distant metastases.

For those with high-risk disease, the aim of the treatment is to achieve TSH suppression at the level of <0.1mIU/L by giving levo-thyroxine (LT_4) supplementation therapy, which is a synthetic version that mimics the endogenously produced thyroid hormone thyroxine (T4). While on LT_4 therapy, the serum Tg levels are monitored 3-6 monthly for 3 years and then once every year. TSH suppression is recognised as an important foundation for DTC treatment, particularly for paediatric patients who are stratified as high-risk for developing recurrence.[9]

A patient with cervical nodal or extensive locoregional disease that is not amenable to surgery, and those having distant metastases are indicated to receive RAI therapy. In the group with the intent to treat using RAI (normally those who are in the intermediate-risk and high-risk groups), TSH-stimulated Tg (attained by temporarily withholding LT_4), and diagnostic ^{123}I WBS or ^{131}I WBS findings are monitored. Furthermore, 6-12 monthly ultrasound neck surveillance is also recommended.[8]

Studies pertaining to RAI therapy for paediatric DTC have been published from America, Europe, South Asia, and West Asia.[10-14] However, there are no reports currently available from Malaysia. Thus, the aim of this study was to determine the clinical and pathological features of the paediatric DTC patients that were referred to the Nuclear Medicine Department of Hospital Kuala Lumpur (HKL), a tertiary referral centre in Malaysia and to assess the treatment response and outcome after administration of RAI.

MATERIALS AND METHODS

Study design

This is a retrospective, longitudinal cohort study, of consecutive paediatric DTC patients who had received treatment in HKL between the period of 1st January 2000 to 30th June 2016. The method adopted was convenience sampling. Thus, all the paediatric patients with operated DTC who were referred to us were recruited during the sampling period. The clinicopathological data and treatment information of the patients were retrieved from the clinic database, whereby referrals were received from all over Malaysia.

Our inclusion criteria for subject recruitment were all patients diagnosed with DTC, aged ≤18 years old, and who either underwent total or hemithyroidectomy followed by completion thyroidectomy, with or without neck node dissection and subsequently referred to our department for RAI during the sampling period. Exclusion criteria were patients who defaulted follow-up. Several attempts were made to arrange for reappointment for the defaulters; however, these patients refused follow-up due to logistic reasons. We confirmed that there were no deaths among the defaulters by telephone calls to the families of patients and also checks on hospital registries during the study period.

In our centre, all referrals for RAI therapy were vetted by our team of nuclear medicine physicians. The policy for institution of therapy is that all operated DTC patients will be administered with RAI for remnant ablation or therapy for cervical nodal or distant metastases. Furthermore, based on the evaluation of multifocality, bilateral lobe involvement, and potential for ETE these factors would influence the decision to treat with RAI.

Baseline blood investigations were also done before giving RAI therapy, which included serum Tg and anti-Tg, and Thyroid Function Test, i.e., T4 and TSH. We ensured that the TSH level was well stimulated > 30mIU/L. Other blood tests prior to giving RAI included checking for the Full Blood Count, Renal Profile, Liver Function Test, as well as serum calcium and phosphate levels.

We administered RAI therapy based on administering a fraction of the recommended adult dose, which is the empirical fixed-dose technique using 3700–7400 MBq (100–200 mCi) ^{131}I. Hence, we adjusted the recommended ^{131}I adult dose to a fraction of the dose, taking into consideration the paediatric patient's age and body weight.

Post therapy WBS was performed at least 3 days post RAI to evaluate the extent of the disease. If the disease was localised, the patient was followed-up with a diagnostic WBS with stimulated serum Tg level monitoring in 6 months. If there was no evidence of disease (NED)/ remission, the patient was followed up every 6 months by monitoring the serum Tg levels alone.

Conversely, if there was evidence of metastatic disease on post therapy WBS, further RAI doses were given at a 6 - 12 monthly interval. Current practice, is that if the cumulative administered RAI dose exceeds 600mCi, the interval of RAI is spaced out and other treatment strategies are actively sought, e.g., re-surgery. Prior to adapting some of the ATA 2015 guideline recommendations, patients with persistent disease that was not amenable to surgery were continued with multiple RAI doses. Nevertheless, from 2016 onwards, patients who demonstrated stable persistent disease were treated with TSH suppression alone and cessation of RAI, especially when the cumulative dose exceeded 600 – 1000 mCi. In the instance of markedly elevated serum Tg, an effort to exclude dedifferentiated disease was made by performing ^{18}F-Fluorodeoxyglucose positron emission tomography/ computed tomography (^{18}F-FDG PET/CT) scans for selected patients.

This study received ethical clearance from the Malaysian Medical and Research Ethics Committee (MREC) [Ethical clearance reference number: NMRR-16-1310-31677 (IIR)].

Data collection

The extracted data included the patients' demographic information, type of surgical history, tumour histology, tumour size based on direct microscopic measurements of the tumour margin, initial staging and risk assessment, RAI therapy history, and imaging history. Among the clinicopathological information extracted included the presence of ETE. ETE was defined as tumour cells that invaded beyond the thyroid capsule into perithyroid soft tissue or organs. Multifocality was recorded, which was defined as more than one focus of cancer in a single thyroid lobe. Moreover, the presence of unilateral vs. bilateral DTC was also recorded. We extracted data for the number of lymph nodes microscopically examined and the number of nodes positive for metastatic disease. Information on the dose and frequency of administering RAI was also recorded.

Post RAI therapy, the patients were classified as having: (1) no evidence of disease (NED) / remission, (2) persistent disease that included stable and dedifferentiated disease, (3) recurrent disease and (4) progressive disease (PD). NED was defined as a negative diagnostic ^{131}I WBS, performed 6 months following RAI with negative serum Tg. Stable disease was defined as a positive ^{131}I WBS at follow-up with similar or less iodine-avid disease than the initial scan. In certain patients with negative ^{131}I WBS despite having rising serum Tg (> 10ng/mL), dedifferentiated disease was suspected based on the ^{18}F-FDG PET/CT scan. Recurrence was defined as locoregional recurrence or distant metastasis detected by ^{131}I WBS or other imaging modalities, after an initial period of being disease-free or NED. Whereas, PD was defined as evidence of increasing number of foci of iodine-avid disease in a ^{131}I WBS or any imaging that fulfilled the Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[13]

Statistical analysis

Statistical analysis was performed using SPSS V22.0. Descriptive statistics displayed the demographic data of the cohort. Continuous data was described using the minimum and maximum values, and the mean and standard deviation (SD). Kruskal–Wallis test and chi-squared test were used to compare categorical and continuous variables. Baseline characteristics were compared using Pearson's correlation for continuous variables and chi-square test for categorical variables. The association between categorical and continuous data with disease status at presentation was assessed using chi-square and Kruskal-Wallis test (for non-parametric data) and Pearson's correlation (for parametric data). A p-value of < 0.05 was considered statistically significant.

RESULTS

Initially, 67 patients fulfilled the study criteria; however, 2 patients defaulted follow-up. Hence, 65 patients were analysed. The characteristics of patients are detailed in Table I. Majority of the patients were females (51/65; 78.5%). The mean age at diagnosis was 14.9 ± 3.7 years (range 4 – 18 years). All the patients underwent thyroid surgery, which included TT in 22 patients (33.8%), TT and CND in 30.8%, and staged surgery in the remaining 35.4% of patients. Fifty patients (76.9%) had classical papillary thyroid carcinoma, 6 patients (9.2%) had follicular variant of papillary thyroid carcinoma and 6 patients (9.2%) had follicular thyroid carcinoma. There were 3 patients (4.6%) with mixed follicular and papillary thyroid carcinoma, well differentiated thyroid carcinoma NOS, and microcarcinoma with evidence of multifocality, bilateral lobe involvement, and tumour close to the surgical margin, respectively. Thirty (46.2%) patients were classified as group N0, 10 patients (15.4%) as group N1a, and 25 (38.5%) as group N1b.

All the DTC patients received treatment with at least one dose of RAI. Of the 65 patients, 13 of them had only remnant disease at the thyroid bed, whereas 33 patients had locoregional disease detected after the first RRA. There were 19 (29.2%) patients with high-risk (M1 stage of disease). Almost all the patients in the M1 group presented with distant metastases to the lungs (94.7%), except for one patient who had metastasis to the bones alone. There were 24 (36.9%) patients stratified as low-risk, 10 (15.4%) patients as intermediate-risk and 31 (47.7%) patients as high-risk, based on the 2015 ATA classification.

Distant metastasis at presentation was significantly associated with pre-pubertal age (p=0.002), presence of cervical lymphadenopathy at initial presentation (p=0.018), bilateral thyroid lobe cancers/ multicentric DTC (p=0.015), multifocal malignancy (p=0.021), ETE (p=0.006), and presence of lymphovascular invasion (p=0.001), as shown in Table II. Large tumour size of >4cm but with no evidence of ETE did not carry any significant risk of metastatic disease at presentation (p=0.131).

The mean time to first RAI therapy after completion of surgery was 96 days. The mean number of times for RAI per patient was 4.26 ± 3.4 (1 -16 times). In several selected patients who had persistently positive post-treatment ^{131}I WBS, RAI therapy was repeated within 6 – 12 months after their initial treatment with RAI (Figure 1). All patients were placed on TSH suppression therapy following RAI. The cumulative RAI dose (CRD) was 30-2040 mCi (mean±SD: 469.8±449.4 mCi). Difference in mean CRD in the remission and persistent disease group was significant (p=0.010), i.e., 297±328 mCi and 729±487 mCi, respectively.

No mortality was reported during our study period. Overall, there were 39/65 (60%) of patients who achieved remission. Among the patients who achieved remission, 49% were from low-risk, 15% from intermediate-risk and 36% from high-risk groups, respectively. Meanwhile, 40% had persistent disease. Twenty-one out of 26 patients in the persistent disease group showed stable disease: 12 patients had persistent locoregional disease, and 9 had persistent lung metastasis. The remaining 5 patients in the persistent disease group had rising Tg levels and negative ^{131}I scans. These patients underwent ^{18}F-FDG PET/CT scans and were identified to have dedifferentiated disease, as shown in Figure 2. Persistent disease was significantly correlated with distant metastasis at presentation (p=0.025). There were no patients detected with recurrence or progressive disease.

Long term adverse events were reported in 2 patients who developed bone marrow suppression, i.e., in one patient with

Table I: Demographics and clinicopathological characteristics among paediatric DTC

Characteristics	Total patients n=65	
	n	% of total
DEMOGRAPHICS AND CLINICAL CHARACTERISTICS		
Gender		
Male	14	21.5
Female	51	78.5
Age at diagnosis (range)	14.9 years ± 3.7 (4- 18)	
Age group		
< 10 years old	7	10.8
≥ 10 years old	58	89.2
Ethnic		
Malay	49	75.4
Chinese	8	12.3
Indian	4	6.2
Others	4	6.2
Presenting complaint		
Thyroid nodule	50	76.9
Cervical lymphadenopathy	7	10.8
Thyroid nodule and cervical lymphadenopathy	7	10.8
Others (e.g., syncopal attack)	1	1.5
Family history of thyroid cancer		
Yes	6	9.2
No	59	90.8
Surgery		
Total thyroidectomy and neck dissection	20	30.8
Total thyroidectomy	22	33.8
Staged surgery (Hemithyroidectomy followed by completion)	23	35.4
HISTOPATHOLOGICAL		
Tumour histology		
Papillary thyroid carcinoma	50	76.9
Follicular thyroid carcinoma	6	9.2
Follicular variant of papillary thyroid carcinoma	6	9.2
Microcarcinoma	1	1.5
Others	2	3.1
Bilateral lobes involvement		
Yes	23	35.4
No	42	64.6
Focality		
Multifocal	30	46.2
Unifocal	35	53.8
Tumour size		
T1a	1	1.5
T1b	23	35.4
T2	16	24.6
T3	21	32.3
T4a	4	6.2
T4b	-	-
Extrathyroidal extension		
Yes	4	6.2
No	61	93.8
Lymphovascular invasion		
Yes	42	64.6
No	23	35.4
Regional nodes metastasis		
N0	30	46.2
N1a	10	15.4
N1b	25	38.5

Footnote: Categorical variables are represented as number (n) and percentage (%). Continuous variables are represented as mean±SD. T: tumour staging. N: lymph node staging.

Table II: Factors associated with distant metastasis at presentation

Clinicopathological characteristics	Total (n=65)		Distant metastasis at presentation				p value
	No	%	No (n=46)	Yes (n=19)			
			No	%	No	%	
Male gender	14	21.5	9	19.6	5	26.3	0.529
Malay race	49	75.4	36	78.3	13	68.4	0.591
Age group < 10 years old	7	10.8	1	2.2	6	31.6	0.002
Presenting with Cervical lymphadenopathy	14	21.5	6	13.0	8	42.1	0.018
Family history of thyroid cancer	6	9.2	4	8.7	2	10.5	0.571
Tumour histology							
Follicular thyroid carcinoma	6	9.2	5	10.9	1	5.3	0.662
Bilateral thyroid lobes involvement	23	35.4	12	26.1	11	57.9	0.015
Multifocality	30	46.2	17	37.0	13	68.4	0.021
Tumour size >4cm	25	38.5	15	32.6	10	52.6	0.131
Extrathyroidal extension	4	6.2	0	0	4	21.1	0.006
Lymphovascular invasion	42	64.6	24	52.2	18	94.7	0.001

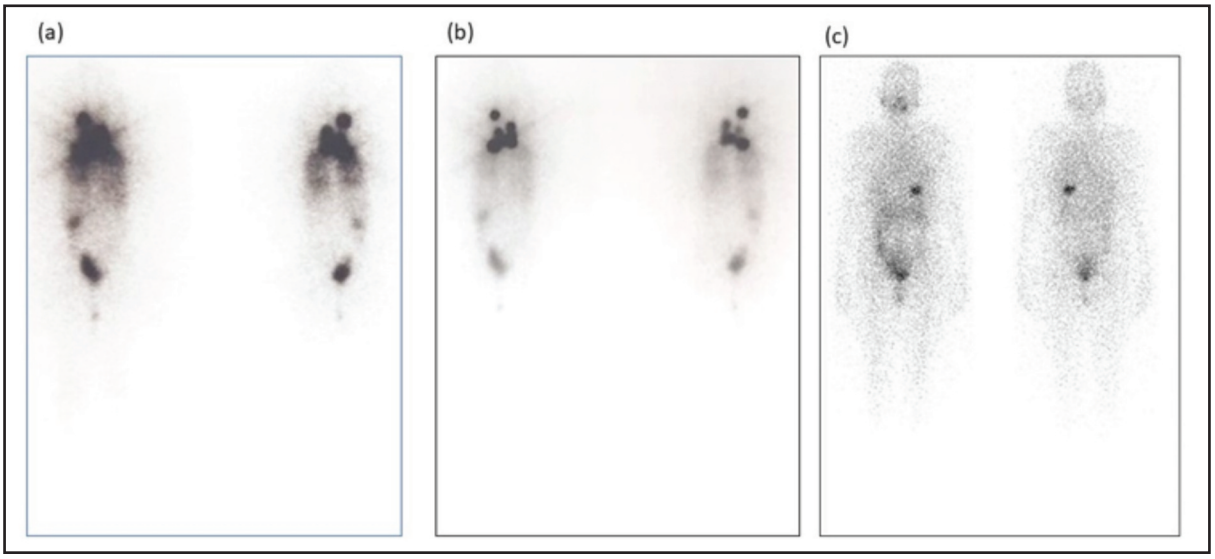

Fig. 1: (a) A 4-year-old girl with papillary thyroid carcinoma having cervical nodal metastasis, who underwent total thyroidectomy and modified right neck dissection. At presentation there was intense locoregional disease with diffuse lung metastasis on the ^{131}I WBS (Serum thyroglobulin, Tg was 50 ng/mL). (b) ^{131}I WBS for the same patient after the 3rd RAI therapy showed reduced tracer uptake in the thyroid bed, cervical nodes and lung indicating response to treatment. (Serum Tg became reduced to 24 ng/mL). (c) ^{131}I WBS after the 5th RAI therapy, with a cumulative dose of 150 mCi, showed physiological uptake, indicative of complete metabolic response. (Serum Tg dropped to < 1 ng/mL).

a total CRD of 2040 mCi and another in a patient with a total CRD of 1080 mCi. Nevertheless, the bone marrow suppression spontaneously resolved several months after the cessation of RAI therapy. Throughout their follow-up, a total of eleven patients underwent other adjunct therapy in addition to RAI therapy, namely eight patients underwent surgery for lymph node excision, and three patients underwent radiotherapy to the neck. One out of these 11 patients underwent RAI 16 times and had radiotherapy to the neck, followed by surgical excision of the neck nodes. Subsequently, this patient was referred to the National Cancer Institute in Putrajaya, Malaysia, for dosimetry-guided RAI of 500 mCi in a single dose. This patient had a total CRD of 1570 mCi. Despite having persistent disease, the patient was asymptomatic throughout and did not have any complications. Whereas, out of the 11 patients, two patients had undergone both radiotherapy and lymph node excision. Another patient with refractory disease, i.e. had persistent lung metastasis despite being administered with 8 consecutive doses of RAI, required dosimetry-based therapy of 300 mCi.

DISCUSSION

Treating paediatric DTC with RAI therapy frequently poses a challenge to physicians in nuclear medicine. There are many controversies pertaining to the factors that affect the risk of recurrence and the most appropriate treatment protocol for them. In our study population, the distribution of tumour histology that was predominantly papillary thyroid cancer and the high female-to-male ratio (5:1); are considered relatively consistent with data from other countries.[11,14,15] Although females acquired DTC more frequently than males, the latter group was noted to have an increased, albeit statistically non-significant risk for developing metastasis, similar to that noted by Kammori et al., 2015.[14]

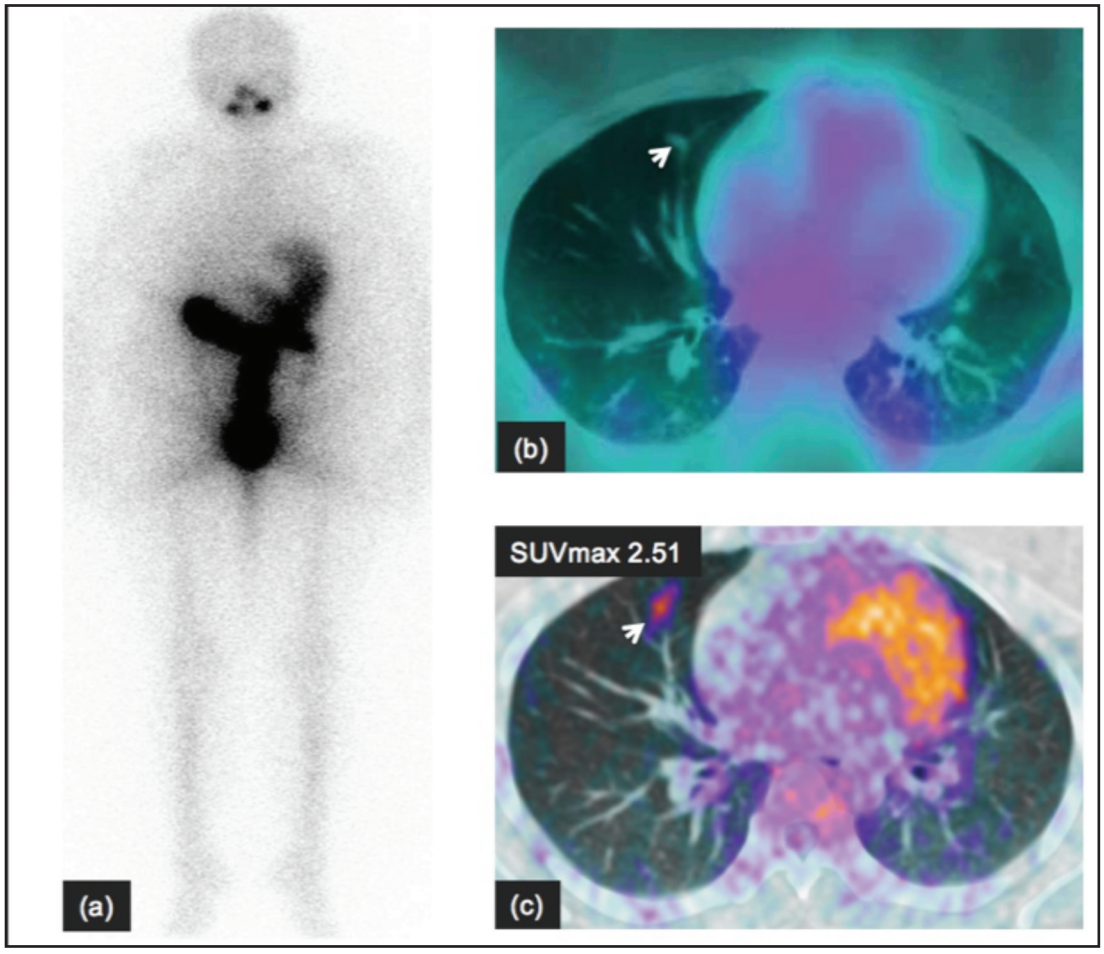

Fig. 2: (a) A 18-year-old patient with negative ^{131}I WBS despite high Tg levels. (b) A small, hypodense lung nodule (arrow) detected in the right middle lobe did not demonstrate tracer uptake on the ^{131}I SPECT/CT scan. (c) ^{18}F-FDG PET/CT scan revealed increased tracer uptake in the small lung nodule at the right middle lobe (SUVmax 2.5), indicative of dedifferentiated disease.

We noted that the distribution of patients based on risk assessment was 36.9% for low-risk, 15.4% for intermediate-risk and 47.7% for high-risk groups, respectively. This distribution is slightly different from a study published by Bhavani et al. 2018 regarding an Indian patient population, which reported that 12% of patients were from low risk, 68% of patients from intermediate risk and 20% of patients from high-risk groups, respectively.[10]

We administered RAI therapy based on an empirical dose whereby we adjusted the ^{131}I dose according to the body weight of patients. We gave a fraction of the dose based on the typical adult activity used to treat similar disease extent, considering the paediatric age and body weight of patients. We practised RRA at HKL for all cases irrespective of the initial risk assessment due to several factors. Firstly, some of our patients were referred to us from remote areas of Malaysia. Hence the patients may not have the benefit of a high-volume thyroid surgeon. Secondly, ^{123}I is not available in Malaysia, limiting our ability to perform an initial diagnostic scan as per the 2015 ATA guideline recommendations. Alternatively, we decided against performing a diagnostic scan using ^{131}I for our patients because it generally confers a higher radiation dose while having a relatively inferior sensitivity to detect disease.[9] Apart from that, the unavailability of post-operative Tg results made RRA a better option for these patients. Furthermore, based on the ATA recommendations in 2015, we practised a modified individualized approach, in which we incorporated the clinicopathological data to guide our approach in the therapy.[9] This included dose modifications by giving a fraction of the adult doses that were based on our personal experiences in paediatric practice.

The pre-pubertal age group had more advanced disease compared to the adolescent group, wherein the majority (85.7%) of patients had distant metastases at presentation. The sites of metastases were predominantly the lungs. This observation was also similar to studies conducted in India and Japan, where there was a high incidence of pulmonary metastases detected at presentation.[3,16] During the course of the treatment, the mean CRD of 469.8 mCi was prescribed for the whole study sample, with the mean CRD in the remission group being significantly lower than in the persistent disease group, i.e., 297±328 mCi and 729±487 mCi, respectively ($p<0.05$). The high CRD is due to the historical practice in HKL with a low threshold of successive RAI administrations, which has already evolved in recent years to be more in line

with the latest clinical practice guidelines. Currently, alternative treatment strategies are usually actively sought in cases that are refractory to RAI therapy. These patients are more likely to continue TSH suppression therapy alone with cessation of RAI.

In addition to RAI therapy, eleven patients had other adjunct treatment in the form of repeat MRND and external beam radiotherapy to the neck. Approximately 60% of the total patients had achieved complete remission. Unfortunately, 40% had persistent disease despite multiple RAI therapies and a multimodality treatment approach. Two patients with lung metastases had ^{131}I internal dosimetry and were given as high as 500mCi in a single dose. Despite high RAI doses to the lungs, no lung fibrosis was reported. No disease recurrence was reported in successfully treated patients. Furthermore, there was neither mortality nor any significant morbidity reported among our patients.

In our study population, the low-risk group's remission rate was higher than the high-risk group. The remission rate for patients having regional nodal metastases and distant metastases was 57.6% and 36.8%, respectively. In cases of iodine avid distant metastasis requiring multiple ablations, radioiodine administration based on the dosimetry approach should be strongly encouraged. We now recognise that dosimetry should be performed early, as RAI refractoriness is defined as CRD >600mCi. Hence, once the paediatric patients have exceeded this limit, the chances are that performing dosimetry prior to giving subsequent RAI may not be remarkably beneficial.

Furthermore, during the study period, no second malignancy was identified or reported. We routinely followed up the patients with thorough history taking, and physical examinations. Additionally, a full blood picture or peripheral blood film investigation was done for patients who had >600 mCi of total cumulative doses of RAI. Nevertheless, a longer duration of study may actually be needed to evaluate the stochastic effects of radiation.

Several selected patients benefitted from ^{18}F-FDG PET/CT scans to help assess their status of dedifferentiated disease. ^{18}F-FDG PET/CT involves the utility of non-invasive hybrid imaging using a glucose analogue radiotracer that can help to diagnose, monitor treatment, and aid in the prognostication of cancers.[17] Based on PET Response Criteria in Solid Tumours (PERCIST) 1.0, the maximum standardised uptake value (SUV_{max}), which is the measured activity of the radiotracer in a given volume of interest in the body, can be recorded from the ^{18}F-FDG PET/CT scans to determine abnormal glucose metabolism in cancerous cells.[18] Dedifferentiated DTC are more aggressive, as they develop a reduction of the sodium iodide symporter and manifest an overexpression of the GLUT1 transporter, thus becoming radioiodine refractory but more metabolically active on ^{18}F-FDG PET/CT scans.[19] Hence, there is a role for referral of patients for a ^{18}F-FDG PET/CT scan if they demonstrate persistently elevated serum Tg, but with relatively low to nil evidence of iodine-avid disease on ^{131}I WBS.[20] After identifying non-RAI avid lesion on ^{18}F-FDG PET/CT imaging, it is necessary to evaluate the feasibility of surgical or oncological therapy because these lesions are at risk of PD.

The limitation of this study is the relatively small overall sample size. Furthermore, as the condition is rare, we had a small proportion of pre-pubertal age group patients with DTC. Although the pre-pubertal age has been reported as a significant factor in previous studies, we were not able to evaluate this factor adequately due to our small sample size. In future, we recommend that efforts need to be taken to obtain more data of children treated for DTC in Malaysia. There is a need to perform multicentre studies to achieve more comprehensive information regarding DTC among children in this country. We also recommend future studies to recruit more subjects from the pre-pubertal age group to evaluate their treatment prognosis. Both gender and pubertal status should be considered in future studies when evaluating iodine-refractory disease. We also recommend that dosimetry-based RAI therapy be instituted early in the treatment protocol, especially when dealing with high-risk patients. Thus, particularly in pre-pubertal children who are more prone to develop marrow suppression and induction of secondary cancers, appropriate management strategies can be developed to achieve better treatment outcome. Furthermore, larger longitudinal studies are needed to determine the long-term survival and the sequelae of radionuclide therapy among the paediatric population.

CONCLUSION

This is the first report on the Malaysian experience in the management of paediatric DTC from the nuclear medicine perspective. Paediatric DTC manifests with more extensive disease at presentation and requires multiple RAI doses. Despite this, it carries an excellent overall prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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