



Combined Maximum Tolerated Activity and Lesion-based Dosimetry for Personalized Radioiodine Therapy in Metastatic Differentiated Thyroid Carcinoma: An Early Institutional Experience

Metastatik Diferansiye Tiroid Karsinomunda Kişiselleştirilmiş Radyoiyot Tedavisi için Maksimum Tolere Edilen Aktivite ve Lezyon Bazlı Dozimetrinin Kombine Edilmesi: Kurumumuzun Erken Dönem Deneyimi

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Hospital Kuala Lumpur, Clinic of of Nuclear Medicine, Kuala Lumpur, Malaysia

Abstract

Objectives: Empirical fixed-activity radioiodine (RAI) therapy remains widely used in differentiated thyroid carcinoma (DTC), despite substantial inter-patient variability in iodine kinetics. Pre-therapeutic dosimetry offers a personalised approach by estimating radiation exposure to organs at risk as well as to tumour lesions. To describe our institutional experience with combined maximum tolerated activity (MTA) and lesion-based dosimetry in patients with metastatic or recurrent DTC, and to evaluate its impact on clinical decision-making.

Methods: A retrospective case series of six DTC patients undergoing pre-therapeutic Iodine-131 dosimetry over two years was recorded. Whole-body and blood-based dosimetry were used to calculate MTA, while lesion-based dosimetry was calculated via estimated absorbed lesion-based dose per administered activity (LDpA). Treatment decisions were made following multidisciplinary discussion.

Results: Five patients completed the dosimetric evaluation. In one patient with high tumour burden, MTA and LDpA provided complementary safety and efficacy data, although facility constraints had limited the final administered activity. In three patients with small-volume inoperable cervical nodal disease, LDpA was <5 Gy/GBq, predicting a limited therapeutic benefit thus preventing further ineffective RAI therapy administration. In another patient with osseous metastases, prior high cumulative RAI exposure as well as low LDpA indicated limited benefit in further high dose RAI therapy, highlighting the importance of early dosimetric assessment.

Conclusion: Personalised dosimetry with combined safety-based and lesion-based approach may enhance the therapeutic precision in patients with advanced DTC. However, careful patient selection is essential in maximising clinical utility.

Keywords: Dosimetry, metastatic differentiated thyroid carcinoma, MTA, lesion-based dosimetry

Address for Correspondence: Nadiah Abd Razak, Hospital Kuala Lumpur, Clinic of of Nuclear Medicine, Kuala Lumpur, Malaysia

E-mail: nadiah.abdrzak@yahoo.com **ORCID ID:** orcid.org/0000-0003-4268-1214

Received: 08.04.2026 **Accepted:** 28.06.2026 **Publication Date:** 06.10.2026

Cite this article as: Razak NA, Lee HMJ, Mathew LA, Hassan SZA, Hairuman H. Combined maximum tolerated activity and lesion-based dosimetry for personalized radioiodine therapy in metastatic differentiated thyroid carcinoma: an early institutional experience. Mol Imaging Radionucl Ther. 2026;35(3):211-222.



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Öz

Amaç: Ampirik sabit aktiviteli radyoaktif iyot (RAI) tedavisi, iyot kinetiğinde hastalar arası belirgin değişkenlik bulunmasına rağmen diferansiye tiroid karsinomunda (DTK) yaygın olarak kullanılmaya devam etmektedir. Tedavi öncesi dozimetri, risk altındaki organların yanı sıra tümör lezyonlarının maruz kalacağı radyasyon dozunu tahmin ederek kişiselleştirilmiş bir yaklaşım sunmaktadır. Bu çalışmanın amacı, metastatik veya rekürren DTK'li hastalarda maksimum tolere edilebilir aktivite (MTA) ile lezyon bazlı dozimetrenin birlikte kullanımına ilişkin kurum deneyimimizi sunmak ve bu yaklaşımın klinik karar verme süreci üzerindeki etkisini değerlendirmektir.

Yöntem: İki yıllık bir süre boyunca tedavi öncesi iyot-131 dozimetresi uygulanan altı DTK hastasının retrospektif olgu serisi değerlendirildi. MTA'nın hesaplanmasında tüm vücut ve kan bazlı dozimetri kullanılırken, lezyon bazlı dozimetri, uygulanan aktivite başına tahmini absorbe lezyon dozu (LDpA) üzerinden hesaplandı. Tedavi kararları multidisipliner değerlendirme sonrasında verildi.

Bulgular: Beş hasta dozimetri değerlendirmesini tamamladı. Yüksek tümör yüküne sahip bir hastada MTA ve LDpA, güvenlik ve etkinlik açısından birbirini tamamlayan veriler sağladı; ancak tesisin fiziksel kısıtlılıkları uygulanabilecek nihai aktiviteyi sınırladı. Küçük hacimli, opere edilemeyen servikal nodal hastalığı bulunan üç hastada LDpA <5 Gy/GBq olarak saptandı ve bunun sınırlı terapötik yarar öngördüğü değerlendirildi. Böylece, etkisiz olması beklenen ilave RAI tedavilerinin uygulanmasından kaçınıldı. Kemik metastazları bulunan başka bir hastada ise daha önce alınmış yüksek kümülatif RAI aktivitesi ve düşük LDpA değeri, ilave yüksek aktiviteli RAI tedavisinden elde edilecek yararın sınırlı olacağını gösterdi ve erken dönemde dozimetri değerlendirmesinin önemini ortaya koydu.

Sonuç: Güvenlilik temelli ve lezyon bazlı yaklaşımların birlikte kullanıldığı kişiselleştirilmiş dozimetri, ileri evre DTK'li hastalarda tedavinin hassasiyetini artırabilir. Bununla birlikte, klinik yararın en üst düzeye çıkarılabilmesi için uygun hasta seçimi büyük önem taşımaktadır.

Anahtar Kelimeler: Dozimetri, metastatik farklılaşmış tiroid karsinomu, MTA, lezyon bazlı dozimetri

Introduction

Thyroid cancer is the ninth most common malignancy worldwide, with approximately 586,000 new cases reported globally (1). Over recent decades, the incidence of thyroid cancer has risen substantially, increasing from 4.9 per 100,000 population in 1975 to 14.3 per 100,000 in 2015. This trend is largely attributed to earlier detection and improved diagnostic modalities, particularly due to the widespread use of high-resolution imaging (2). Thyroid cancer demonstrates a marked female predominance, with incidence rates approximately three times higher in women than in men, estimated at 10.1 per 100,000, and accounting for nearly 1 in every 20 cancers diagnosed among women worldwide (1). Established risk factors for thyroid cancer include exposure to ionising radiation, as well as excess body weight, increased height, hormonal influences, and certain environmental pollutants (1). The vast majority of thyroid malignancies with more than 90% are classified as differentiated thyroid carcinoma (DTC), encompassing papillary, follicular, and oncocytic (Hürthle cell) carcinoma (2).

The standard management of DTC consists of surgical resection, followed by radioiodine (RAI) therapy and thyroid stimulating hormone (TSH) suppression. In cases of RAI-refractory DTC, alternative treatment modalities such as external beam radiotherapy or systemic targeted therapies, including multikinase inhibitors may be considered (2). RAI therapy is administered with the intent of thyroid remnant ablation, adjuvant treatment, or for treatment of known residual or metastatic disease. In patients with DTC who present with known distant metastases at initial diagnosis, RAI therapy is routinely recommended following

total thyroidectomy. Two principal strategies for activity prescription are typically employed; most commonly practiced being empirical fixed-activity administration, with the latter being dosimetry-based therapy (2).

Despite its widely preferred strategy of therapy due to its ease of use and generally favourable outcomes, the RAI empirical fixed activity unfortunately does not account for inter-patient variability. Variability among patients in iodine biodistribution and clearance is influenced largely by multiple factors such as individual renal function, tumour burden, metastatic pattern and prior treatments (2). As a result, fixed-dose strategies may lead to under-treatment in patients with rapid iodine clearance or extensive disease, or conversely excessive radiation exposure in patients with prolonged whole-body retention. This variability is particularly relevant in patients with extensive metastatic disease or diffuse lung metastases, in whom high administered activities are associated with an increased risk of bone marrow suppression, radiation pneumonitis, and pulmonary fibrosis (2).

On the other hand, pre-therapeutic RAI dosimetry offers individualised administered activity by estimating patient-specific radiation exposure to critical organs and target tissues. This is performed through the calculation of iodine kinetics via serial measurements, selecting the administered activity that maximises therapeutic efficacy while maintaining exposure within established safety limits. Therefore, in this era of precision medicine, dosimetry has emerged as an important tool in the management of selected patients with DTC, particularly those with metastatic disease, unusual iodine kinetics, or elevated risk of treatment-related toxicity (2).

The pre-therapeutic RAI dosimetry can be broadly categorised into maximum tolerated activity (MTA) and lesion-based dosimetry. MTA as recommended by the European Association of Nuclear Medicine (EANM) are bound to the basic principle of dose-limiting organs (3). They rely on the administration of a tracer activity of iodine, followed by serial whole-body counting and blood sampling to model iodine kinetics and estimate radiation exposure to the bone marrow and lungs, the principal dose-limiting organs. This approach allows calculation of the highest safely administrable therapeutic activity while maintaining radiation exposure below established toxicity thresholds. Lesion-based dosimetry, in contrast, focuses on quantifying the absorbed dose delivered to metastatic or residual tumour tissue using serial planar imaging and single photon emission computed tomography/computed tomography (SPECT/CT)–time-based activity measurements. Although lesion dosimetry provides valuable insight into tumour dose–response relationships and may better predict therapeutic efficacy, its routine clinical application remains limited by methodological complexity, multiple time point imaging requirements, and the lack of standardised absorbed dose targets for tumour control. This study describes our institutional experience using combined MTA and lesion-based dosimetry in selected patients with metastatic or recurrent DTC and evaluates its clinical impact.

Materials and Methods

Study Design and Patient Selection

This retrospective case series included six patients with DTC, referred for pre-therapeutic Iodine-131 (I-131) dosimetry between 2023 and 2025. Patients were selected following multidisciplinary team discussion based on following indications:

Concern for organ-at-risk toxicity with high-risk of bone marrow suppression, as well as pulmonary and renal toxicity

High tumour burden including extensive metastasis or large tumour size

Inoperable recurrent disease

Prior high cumulative RAI exposure

Dosimetry Protocol

All patients received 5 mCi of I-131 after adequate patient preparation with either one month duration of thyroxine withdrawal or injection of the recombinant human TSH (rhTSH). Serial whole-body scans (WBS) and blood sampling were performed at 2, 4, 24, 48, and 120 hours

post-administration for MTA calculation. WBS and regional SPECT/CT imaging were obtained at 1, 4, 24, 48, and 120 hours post I-131 administration for lesion-based dosimetry. MTA was calculated based on established bone marrow dose limits (≤ 200 cGy) and whole-body retention for lung toxicity. Critical lung activity at 48 hours whole-body retention is based on the Benua criterion, calculated using OLINDA 1.1 with this formula:

$$ctivity(t)=A*\exp(-at)+B*\exp(-bt)+C*\exp(-ct)$$

(uptake % all time point)

LDpA was calculated using time–activity curves as well as from lesion-based dosimetry using the HERMES software, which was derived from serial imaging (Table 1). Details of the HERMES software were as below:

Hermes Medical Solutions, Stockholm, Sweden: HybridRecon-Oncology 3.2.0

Fitting model: Mono-exponential, bi-exponential (for voxel–trapezoidal)

Algorithm: Phantom-based (OLINDA /EX 1.1) ORNL adult phantom

Assumptions: Physical half-life correction

There is no uncertainty calculation for the LDpA value in our study. However, the LDpA value was estimated using organ-based dosimetry–Medical Internal Radiation Dose (MIRD), following Walter Jentzen calculation:

Projected ^{131}I residence time (RC-corrected)

$$\frac{LDpA}{\text{Gy/GBq}} = 1.573 \cdot \frac{(\tau_L/\text{min})}{(m/\text{g})} \cdot (1 + 0.136 \cdot \sqrt[3]{m/\text{g}})$$

Lesion mass (using common tissue densities)

Comparison was also made with voxel-based dosimetry using Hermes Voxel Dosimetry.

This retrospective case series has been submitted to the National Medical Research Register (Advancing Medical Research in Malaysia) with the research ID RSCH 1D-26-01243-NC0 for ethical approval on 26 February 2026.

Results

Five patients completed dosimetry protocol. One patient did not complete the protocol due to an intercurrent event.

Patient 1 : High Tumour Burden Case

A 65-year-old gentleman had initially presented with pathological right humeral fracture, and was treated with surgical plating and biopsy. The histopathology of the right humerus biopsy was confirmed to be metastatic follicular

thyroid carcinoma, which he subsequently underwent total thyroidectomy. Histopathology of the thyroid tissue was proven to be widely invasive follicular thyroid carcinoma. Magnetic resonance imaging of the spine demonstrated expansile bone lesions with soft tissue components involving T9 and L4 vertebrae, suggestive of bone metastasis. He then received RAI twice (Figure 1), with a cumulative dose of 300 mCi I-131. WBS post second RAI demonstrated multiple skeletal metastases involving the left scapula, distal right humerus, vertebrae (T9 and L4) as well as proximal right femur. With the persistently high suppressed serum thyroglobulin [2088ng/mL ^{18}F -fluorodeoxyglucose positron emission tomography/CT (^{18}F -FDG PET/CT)] was arranged, revealing ^{18}F -FDG-avid skeletal metastases at the left scapula, vertebrae and pubic bone. Correlating both images, there were presence of mixed iodine- and ^{18}F -FDG-avid metastasis at multiple bones with predominant iodine-avidity.

We proceeded with the calculation of MTA and LDpA targeting the T9 and L4 vertebrae lesions with 5 mCi I-131 after two doses of rhTSH injection. Subsequently, the patient received his third RAI therapy with 300 mCi I-131 (total cumulative dose of 600 mCi I-131) under rhTSH stimulation and steroid cover, which was then tapered down post therapy. Post treatment whole body scan

showed stable I-131 skeletal metastasis in the left scapula, distal right humerus, vertebrae (T9 and L4) as well as proximal right femur, some with lesser intensity of uptake. Repeated ^{18}F -FDG PET/CT done due to persistently high serum thyroglobulin levels showed similar ^{18}F -FDG-avid skeletal metastasis in the left scapula, vertebrae and pubic bone. He was then referred to the oncologist as he was considered as RAI refractory disease, and was started on T. Lenvatinib 14mg OD. Suppressed serum thyroglobulin levels were monitored and showed good response to Lenvatinib, reducing significantly from 36851ng/mL to 1172ng/mL. ^{18}F -FDG PET/CT done a year after the RAI and Lenvatinib initiation showed interval reduction in ^{18}F -FDG-avid skeletal metastasis in the spine of left scapula, vertebral body and left pubic ramus with latest suppressed serum thyroglobulin of 223.00 ng/mL.

Patient 2: Small-volume Inoperable Cervical Disease

A 76-year-old lady with a history of undergoing thyroidectomy in 2003 with no documented histopathology had presented again in 2019 with a complaint of right sided neck swelling. She then underwent right hemithyroidectomy, and the histopathology was consistent with widely invasive follicular carcinoma with extrathyroidal extension. Two years later, she developed recurrent neck swelling and underwent a tumour debulking surgery.

Table 1. Table summary of MTA and LDpA of patients

Patient	MTA			LDpA		
	48-h retention value (%)	Bone marrow toxicity (Gy/GBq)	MTA (mCi)	Calculated LDpA (Gy/GBq)	Estimated activity (mCi)	Estimated absorbed dose (Gy)
Patient 1	4.14	0.0760	711	L1 (T9): 9.18	500	169.90
					400	135.92
					300	101.94
				L2 (L4): 6.10	500	112.86
					400	90.28
					300	67.71
Patient 2	3.17	0.1185	456	1.17	500	21.64
					400	17.32
					300	12.99
Patient 3	5.44	0.0942	574	0.19	500	7.21
					400	5.77
					300	4.33
Patient 4	8.4	0.0750	721	0.38	400	5.59
Patient 5	2.31	0.0526	1028	0.19	500	3.59
					400	2.87
					300	2.15

MTA: Maximum tolerated activity, LDpA: Lesion dose per administered activity

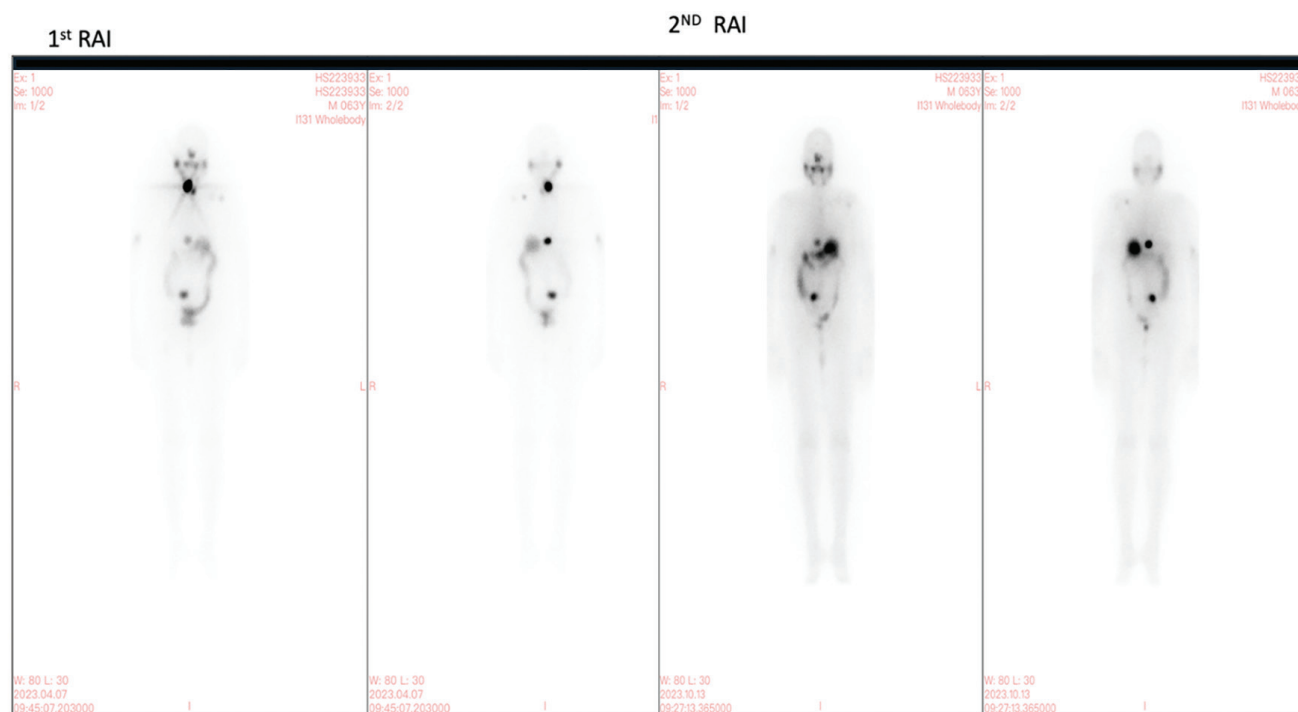


Figure 1. Serial I-WBS of patient 1 who received two times of RAI. I-WBS post second ablation demonstrated multiple skeletal metastases involving the left scapula, distal right humerus, vertebrae (T9 and L4) as well as proximal right femur
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

The histopathology showed recurrent follicular thyroid carcinoma with presence of right internal jugular vein tumour thrombus. The stimulated serum thyroglobulin level was more than 5000ng/mL, thus ^{18}F -FDG PET/CT was arranged, demonstrating ^{18}F -FDG-avid mass in the right thyroid bed measuring up to 4.4cm (maximum standardized uptake value 17.4). This patient received 6 courses of RAI treatment over a period of 4 years (cumulative dosage received was 870 mCi of I-131). During this period, she also underwent her fourth surgical intervention, which was debulking of tumour procedure. Multiple WBS post therapy showed a persistent solitary iodine-avid disease at the lower neck region with consistently raised stimulated thyroglobulin reading of 520ng/mL (Figure 2). Correlating both images, there was a solitary mixed iodine- and ^{18}F -FDG-avid disease at the soft tissue lesion in the right thyroid bed.

We proceeded with calculation of MTA and LDpA with of 5 mCi of I-131 after two doses of rhTSH injection. WBS showed focal increased tracer uptake at the neck corresponding to soft tissue lesion at the right thyroid bed measuring 1.3 x 0.9 cm. LDpA calculation showed extremely low lesion absorbed dose (LDpA 1.17 Gy/GBq). Based on this, it was inferred that the patient would not

benefit from further RAI treatment, and the patient opted for surveillance and TSH suppression therapy.

She was originally on active surveillance with only TSH suppression therapy, and first surveillance ^{18}F -FDG PET/CT done at 1 year interval showed stable disease at the neck. However, serial serum thyroglobulin monitoring showed persistently increasing levels up to 1720ng/mL after 2 years duration. Repeated ^{18}F -FDG PET/CT at 2 years after the last RAI treatment dose demonstrated progressive ^{18}F -FDG-avid disease in the neck with the presence of new ^{18}F -FDG-avid nodal and lung metastases. She subsequently received a trial course of RAI therapy with 150 mCi of I-131, which demonstrated iodine-avid disease in the neck and nodal regions, along with newly identified metastatic involvement of the lungs, liver, and bones. In view of the documented disease progression and retained iodine avidity at the new disease sites, she was scheduled for another RAI ablative therapy.

Patient 3: Small-volume Inoperable Cervical Disease

A 37-year-old lady initially presented with neck swelling for 6 years in duration, which was gradually increasing in size. She underwent total thyroidectomy on 16/6/2022 which showed papillary thyroid carcinoma with pretracheal

nodal metastasis. She received RAI therapy three times between 2021 and 2024, with a total cumulative dose of 340 mCi I-131. The latest post therapy WBS showed similar focal increased uptake in the superior mediastinum, corresponding to the subcentimeter left upper paratracheal node (Figure 3). Stimulated serum thyroglobulin reading was 24.8ng/mL.

We proceeded with calculation of MTA and LDpA calculation after 5 mCi of I-131 on 16/12/2024 under thyroxine withdrawal. WBS done 48 hours post-administration of I-131 showed only faint uptake in the left lower neck region. Lesion-based dosimetry calculation revealed a very low absorbed dose in this lesion (LDpA 0.39 Gy/GBq). In view of the low LDpA, we explained to the patient that there was no benefit in further RAI treatment for such a small volume disease, and the patient was then placed on TSH suppression therapy.

Patient 4: Small-volume Inoperable Cervical Disease With Fertility Issue

38-year-old male, with a history of left sided neck swelling in 2019. He was investigated for suspicious thyroid nodules and eventually underwent total thyroidectomy with left modified radical neck dissection. Histopathology confirmed the diagnosis of papillary thyroid carcinoma with

lymph node metastasis. He has received a total of 7 RAI treatments between the years of 2019 and 2024, totalling 870 mCi I-131. He also underwent right modified radical neck dissection in between RAI therapy in 2022. WBS post 7th RAI treatment demonstrated persistent uptake in the lower neck corresponding to pretracheal lymph node measuring 1.0x1.4cm (Figure 4). Stimulated serum thyroglobulin showed a reduction in trend from the initial figure of 105.4 ng/mL to the latest reading of 11.0 ng/mL.

We proceeded with calculation of MTA and lesion dose per administered activity calculation using 5 mCi of I-131 on 17/3/2025 under thyroxine withdrawal, which showed very poor iodine retention and lesion absorbed dose in the lower neck lesion (LDpA 0.38 Gy/GBq). Subsequently, it was concluded that patient would likely have no significant benefit from continuing with further RAI treatment. This enabled the patient who had been struggling with fertility issues to opt for surveillance and TSH suppression therapy, and to proceed for active fertility assessment and treatment.

Patient 5: Osseous Metastases With High Prior Cumulative RAI

A 41-year-old lady with underlying history of right hemithyroidectomy for multinodular goitre, presented

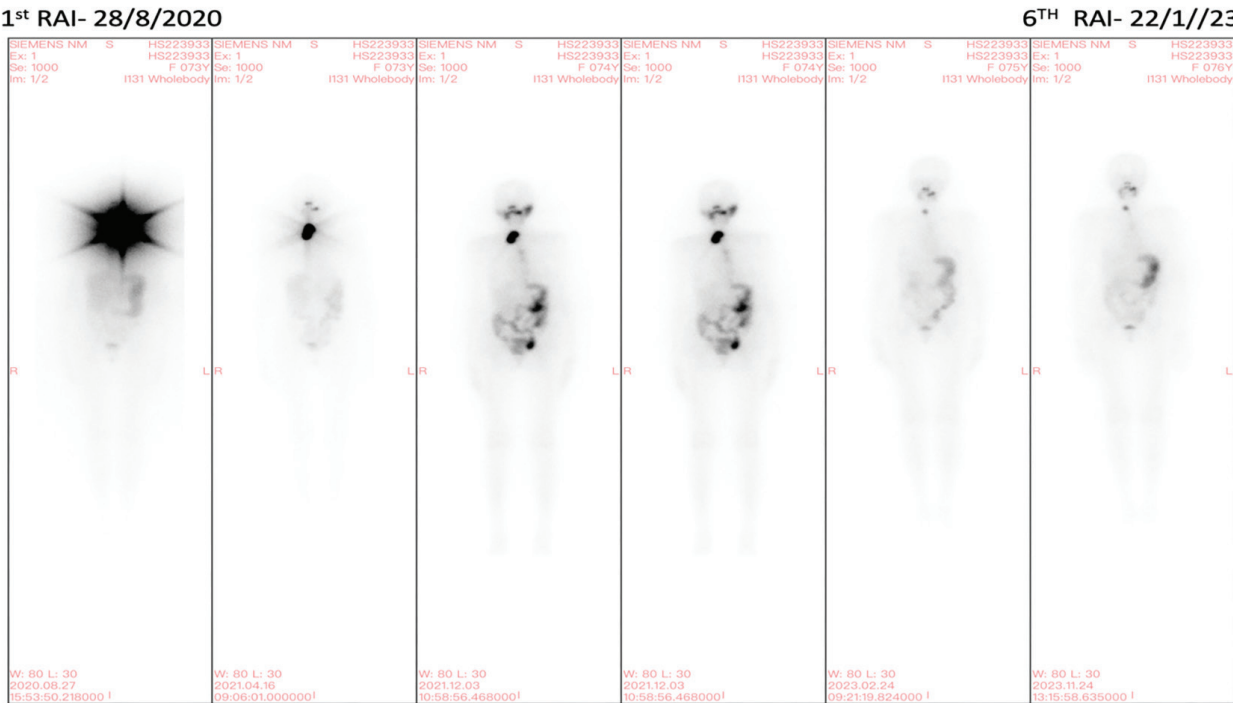


Figure 2. Serial I-WBS of patient 2 who received six times of RAI. I-WBS post six ablation demonstrated persistent solitary iodine-avid disease at the lower neck region
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

with incidental pulmonary nodules on CT during follow-up. Biopsy of the lung nodules was consistent with metastatic follicular carcinoma. Left hemithyroidectomy was performed and the histopathology was consistent with the follicular variant of micropapillary thyroid carcinoma. First few post therapy WBS showed iodine avid disease in the cervical nodes, lungs and bone. She underwent a total of 8 RAI treatments over seven years (cumulative dose 1330 mCi), with the latest WBS post 150 mCi of I-131 showing persistent tracer uptake anterior to the hyoid bone, at L1

vertebra and left proximal femur lytic lesions (Figure 5). Subsequent ^{18}F -FDG PET-CT showed non- ^{18}F -FDG avid lytic bone lesions in the vertebra, right acetabulum and left femur.

We proceeded with calculation of MTA and LDpA with 5 mCi of I-131 after two doses of rhTSH injection. WBS performed showed mild iodine avid metastatic disease at the left femur. LDpA calculation showed significantly low lesion absorbed dose at left proximal femur lesion (LDpA 0.19Gy/GBq). Since monitoring of stimulated serum

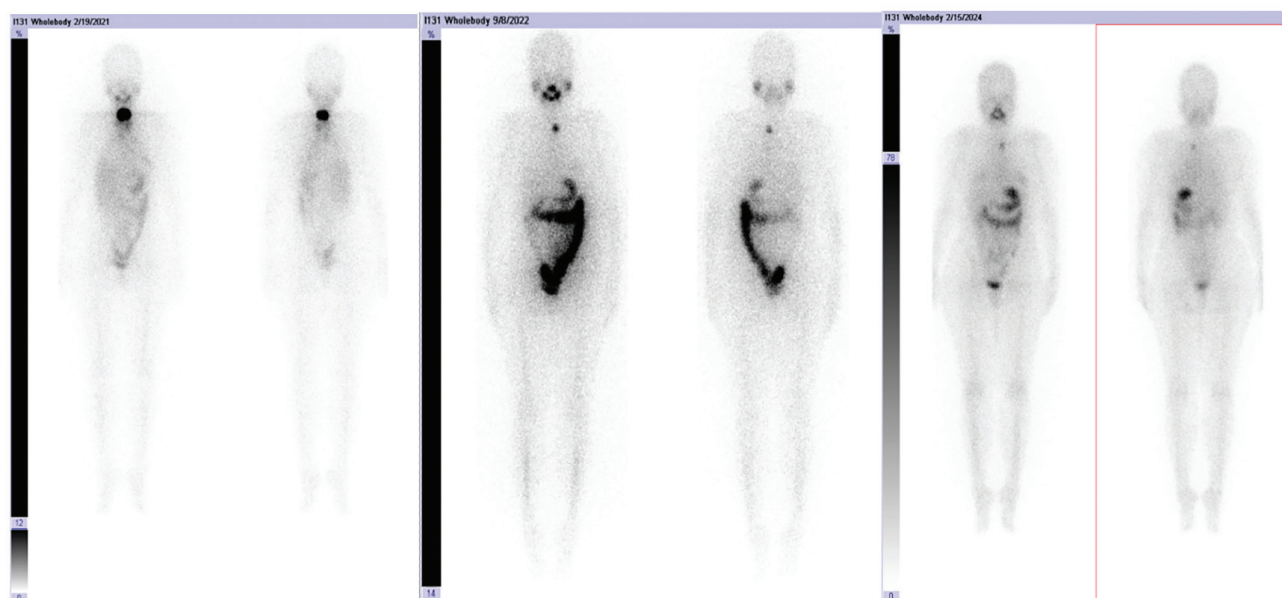


Figure 3. Serial I-WBS of patient 3 who received total of three ablation. I-WBS post ablation demonstrated focal increased uptake in the superior mediastinum, corresponding to left upper paratracheal node
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

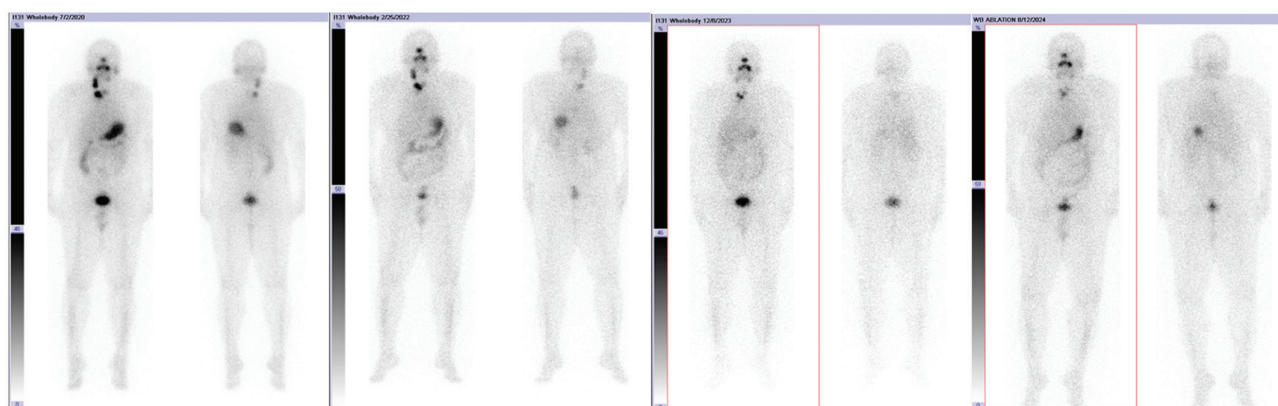


Figure 4. Serial I-WBS of patient 4 who received total of eight ablation (images above are the last 4 I-WBS post ablation). I-WBS post ablation demonstrated persistent uptake in the lower neck corresponds to pretracheal lymph node measuring 1.0 x 1.4 cm
I-WBS: Iodine whole-body scan

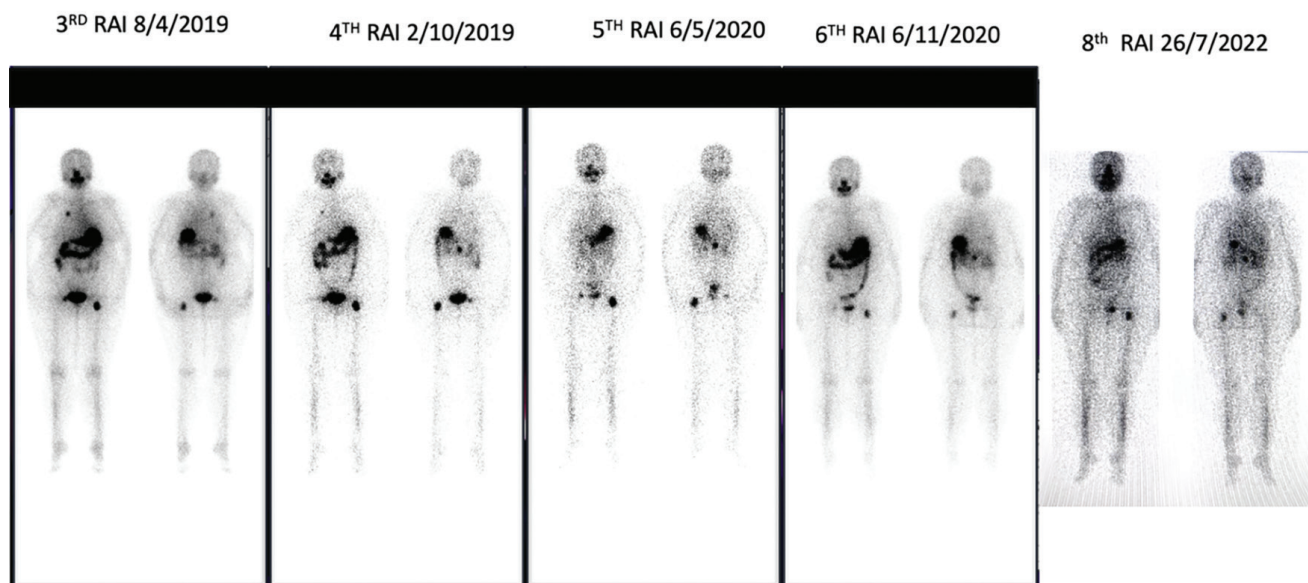


Figure 5. Serial I-WBS of patient 5 who received eight RAI. I-WBS post eight ablation demonstrated persistent tracer uptake anterior to the hyoid bone, at L1 vertebra and left proximal femur lytic lesions
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

thyroglobulin had been stable over the past few years, with the latest serum thyroglobulin reading of 31.2 ng/mL and minimal benefit for further RAI treatments as evidenced by low iodine retention time, the patient opted for TSH suppression therapy and close surveillance with 6 monthly serum thyroglobulin and anti-thyroglobulin monitoring.

Discussion

A total of six patients with DTC underwent pre-therapeutic dosimetry over a two-year period at our center. One patient was unable to complete the procedure due to a low-impact fall at home during the study period, resulting in abandonment of the dosimetric assessment. The remaining five patients successfully completed the protocol. For these patients, both the MTA method and the LDpA calculations were performed.

The primary objective of pre-therapeutic dosimetry is to administer an adequate radiation dose to the target lesions to achieve therapeutic efficacy (curative, disease stabilisation, or palliative intent), while minimising radiation exposure to critical organs in order to reduce the risk of acute and long-term toxicities. In our institution, patient selection for dosimetric evaluation was determined following multidisciplinary team discussion, taking into

consideration patient's disease burden, concern for toxicity to vital organs, and also patient's cumulative RAI treatments and exposure, especially for those with repeated RAI therapy.

Nagarajah et al. (4) demonstrated a correlation between absorbed dose thresholds and complete response rates in metastatic lesions and thyroid remnants. The authors emphasised that different metastatic sites require different absorbed dose targets to optimise therapeutic response. Specifically, bone metastases require an absorbed dose exceeding 85 Gy to achieve approximately 46% response rates, whereas substantially higher absorbed doses (350-650 Gy) are associated with response rates of 70-80% (4). Our first patient presented with high tumour burden with multiple osseous metastases, which were both ^{18}F -FDG and iodine avid. Based on whole-body and blood-based dosimetry, the calculated MTA, without exceeding bone marrow and pulmonary safety thresholds, was 711 mCi of I-131. However, LDpA calculations demonstrated that an administered activity of approximately 400 mCi would only be able to achieve a target absorbed dose of approximately 135 Gy for both T9 and L4 vertebral metastases. This information allows the treating physician to understand that curative intent of treatment may not be attainable as

less than 50% of patients with bone metastasis achieve remission with estimated absorbed doses of 85 Gy (5). However, due to logistical and facility limitations during treatment of our first patient, the maximum administrable activity was restricted to 300 mCi and he was ultimately given the maximum dose at that time which was below the calculated MTA (711 mCi) and below the estimated activity required to achieve optimal absorbed dose for bone metastases. In this patient, although we were able to give a higher than empirical dose of RAI therapy (300 mCi), the LDpA enabled us to adjust our expectations from curative to palliative intent as complete remission might not be achievable in this patient. An early referral to the oncology department was made, and this patient has been doing well after the initiation of systemic therapy (Lenvatinib) which is evidenced by pain reduction and reducing serum Thyroglobulin levels.

The case above highlights the difference between organ-at-risk-limited activity (MTA approach) and LDpA, which is personalised to each individual. These findings also demonstrate the importance of individualised lesion-based dosimetry in patients with high tumour burden, particularly in skeletal metastases where higher absorbed doses may be necessary for optimal therapeutic outcomes. Nagarajah et al. (4) also reported that a target absorbed dose of 85 Gy is associated with treatment response rates of approximately 75% in lymph node metastases and 95% in pulmonary metastases. In contrast, thyroid remnants require substantially higher absorbed doses, exceeding 300 Gy, to achieve response rates of approximately 91%. These findings further support the concept that absorbed dose thresholds vary according to lesion type and anatomical location.

Our second and third patients both who had undergone multiple rounds of RAI treatment initially underwent pre-therapeutic dosimetry with curative intent. Both patients demonstrated persistent RAI uptake in inoperable soft tissue lesions within the neck. Despite visible iodine avidity on previous high dose post therapy whole body scans, lesion-based dosimetry using I-131 of 5 mCi revealed low absorbed dose per administered activity (<5 Gy/GBq) in these subcentimeter lesions, indicating limited therapeutic efficacy from further RAI administration. Jentzen et al. (5), in earlier studies, categorised metastatic lesions into three groups according to LDpA, correlating with probability of therapeutic response. Lesions were stratified into low (<5 Gy/GBq), intermediate (5-10 Gy/GBq), and high (>10 Gy/

GBq) LDpA groups (5). Clinically meaningful response rates were significantly higher when LDpA exceeded 5 Gy/GBq (5). Based on this classification, both the two patient's lesions fell under the low LDpA category, suggesting a low likelihood of achieving curative benefit with additional I-131 therapy. These findings highlight the clinical value of lesion-based dosimetry in identifying patients unlikely to benefit from further RAI treatment, thereby facilitating earlier transition to alternative therapeutic strategies.

Similar to the second and third patients, our fourth patient presented with persistent solitary RAI uptake in the lower neck region corresponding to inoperable cervical nodal metastasis. His previous RAI treatments have demonstrated a concurrent reduction in stimulated serum Thyroglobulin levels, indicating partial success in treatment. However, due to the prolonged and recurrent RAI treatments, he had delayed his family planning despite being married for more than five years. He was verbally informed that there was suspicion of oligospermia. Following multidisciplinary team discussion, lesion-based dosimetry was performed with curative intent. However, the calculated LDpA was markedly low (<5 Gy/GBq), indicating a low probability of achieving meaningful therapeutic response with additional RAI therapy. Consequently, a watchful waiting strategy was adopted with serial serum Thyroglobulin level monitoring. In this patient, findings of the lesion based dosimetry enabled the patient to make an informed decision whereby the patient could make the choice not for further RAI rience of the second, third, and fourth patients, we observed that lesion size appears to play a significant role in dosimetric outcomes. Subcentimeter or small-volume lesions consistently demonstrated low LDpA values, suggesting limited radiation delivery despite visible iodine avidity. This observation highlights an important clinical consideration - that RAI uptake alone does not necessarily translate into sufficient absorbed dose for therapeutic efficacy. From a technical perspective, small-volume disease also presents additional challenges. Accurate tumour delineation during image-based dosimetry is more challenging as it is susceptible to partial volume effects and contouring inaccuracies, potentially leading to under or overestimation of lesion size and inaccuracies in absorbed dose calculation. Even so, there could be underestimation of calculations of LDpA due to the small lesion size, leading to markedly reduced estimated absorbed dose. Partial volume effects in LDpA estimation can be corrected by performing Recovery Coefficients. However, due to the unavailability of a suitable phantom, recovery coefficient measurements

could not be performed at our center during this study period. Consequently, partial-volume correction using recovery coefficients was not incorporated into the current LDpA estimations. As part of future work, phantom-based recovery coefficient determination will be implemented to improve the accuracy and reliability of LDpA estimates in subsequent patients. We also believe that close collaboration between the nuclear medicine physician and medical physicist is essential to ensure precise tumour mapping which will in turn translate into reliable dosimetric assessment.

Our fifth patient presented with three osseous metastases that were delineable on CT imaging. All lesions demonstrated RAI avidity on post ablation WBS without corresponding uptake on ^{18}F -FDG PET/CT, suggesting well-differentiated disease biology and a favorable prognosis for RAI-based therapy. However, as the patient had already received a high cumulative administered activity of RAI well as increased risk of secondary malignancy. Lesion-based dosimetry demonstrated only mild tracer uptake in the left femoral lesion with low LDpA, indicating insufficient radiation delivery to achieve therapeutic benefit. Based on these findings, further RAI therapy was deemed unlikely to provide meaningful clinical response. This case proposes the importance of early dosimetric assessment in patients with potentially curable metastatic disease. Timely implementation of lesion-based dosimetry may help optimise therapeutic strategy before cumulative RAI exposure limits treatment options, thereby maximising the likelihood of achieving adequate absorbed dose to target lesions while minimising unnecessary radiation burden, in which higher cumulative RAI exposure dosage may lead to increased risk of leukaemia or secondary malignancies in short and long-terms (8).

Our dosimetry-based approach is consistent with contemporary guidance from the American Thyroid Association (ATA) and the EANM, which recognises the role of individualised RAI activity selection in selected patients with differentiated thyroid cancer. The ATA guidelines suggests the use of empiric fixed-activity regimens for remnant ablation and many intermediate-risk cases, and proposes the use of whole-body and blood-based dosimetry in metastatic disease to limit bone marrow exposure (≤ 200 cGy) and to avoid excessive whole-body retention (2). Similarly, EANM guidance emphasises the value of personalised absorbed dose estimation in advanced or recurrent disease (3). Earlier study in dosimetry suggested the application of five-point protocol, which is time-

consuming and complex thus making it less favourable among physicians. Although this 5-point protocol is certainly the most accurate, few studies have suggested the use of adapted 24-96 hour approach (5). This two point protocol is recommended when clinical workload is particularly heavy, to reduce logistical and time demands for patients and caregivers as well as the clinical costs (5). A more recent study has validated the use of a simplified dosimetry model to determine the %48-hour fractional whole body retention thus the MTA (6). This simplified dosimetry allows us to calculate the maximum dose activity for the marrow in a more practical method, although it is currently not being advocated as a replacement for full patient-specific dosimetry. Rather, its use is proposed when a more comprehensive dosimetry is not feasible, which this approach could be used to guide the therapist in selecting the I-131 prescribed activity in treating patients with metastatic DTC (7).

Although worldwide I-124 PET/CT is preferred as it is considered superior for thyroid cancer dosimetry due to its higher spatial resolution and improved quantitative accuracy, I-131 was selected as the radiotracer in our centre because of its greater availability and cost-effectiveness. Even though previous studies have demonstrated that I-124 PET provides more accurate quantification for dosimetric purposes (8), emerging evidence has supported the feasibility of I-131 as a diagnostic tracer for pre-therapeutic dosimetry in differentiated thyroid cancer (4). All of our patients had the five time points serial whole body and blood count obtained at 2, 4, 24, 48, and 120 hours following administration of 5 mCi of I-131. In addition, WBS with regional SPECT/CT imaging were performed at 1, 4, 24, 48, and 120 hours post-administration to enable lesion-based dosimetric analysis.

Apart from this, the potential thyroid stunning effect associated with the administration of 5 mCi I-131 during MTA assessment should also be considered. Several studies have reported that diagnostic doses of 5 mCi I-131 may induce clinically significant thyroid stunning, particularly during the early post-diagnostic period, thereby reducing subsequent therapeutic RAI uptake. These reports have suggested a waiting interval of approximately 2-3 months before definitive RAI therapy to allow recovery of iodine-trapping function (9). In consideration of this potential phenomenon, our department elected to schedule RAI ablation therapy approximately three months after MTA calculation to permit gradual recovery of iodine-trapping ability and optimise therapeutic uptake.

This case series demonstrates that although RAI dosimetry is time consuming and requires close collaboration among nuclear medicine physicians, medical physicists, radiopharmacists and technologists, it provides meaningful clinical value in the management of DTC patients. Individualised dosimetric assessment influenced therapeutic decision-making in our cohort by identifying patients likely to benefit from RAI therapy, while sparing others from ineffective and potentially burdensome treatment. Careful patient selection remains crucial to maximise the clinical utility of dosimetry. In our experience, patients with high tumour burden, pulmonary metastases, renal impairment, or high prior cumulative RAI exposure derive the greatest potential benefit from personalised activity planning. Conversely, routine application in low-risk or small-volume disease may not yield significant therapeutic advantage. Overall, personalised RAI dosimetry represents a precision-medicine approach that may optimise therapeutic efficacy while minimising unnecessary radiation exposure. With continued refinement of technique and appropriate patient selection, dosimetry has the potential to play an increasingly important role in the individualised management of advanced thyroid cancer.

Study Limitations

This study is limited by small sample size, retrospective design, heterogeneity in disease presentation, and limited long-term outcome. Larger prospective studies are recommended to validate the LDpA thresholds and to define the standardised tumour absorbed dose targets.

Another limitation of this study is the absence of formal uncertainty quantification for the estimated LDpA values. Although dosimetric calculations were performed using the MIRD organ-based methodology, uncertainties associated with image quantification, ROI delineation, system calibration, and time–activity curve fitting were not propagated into the final dose estimates. Furthermore, partial volume correction was not applied, as recovery coefficients could not be determined due to the unavailability of a suitable calibration phantom at our institution during the study period. As a result, the reported LDpA values may be affected by residual quantification errors, particularly for small lesions. Nevertheless, comparison with voxel-based dosimetry using Hermes Voxel Dosimetry demonstrated comparable dose estimates, providing supportive evidence for the robustness of the findings. Future studies incorporating phantom-derived recovery coefficients and comprehensive uncertainty analyses are warranted to further improve the accuracy and reliability of LDpA estimation.

Conclusion

Pre-therapeutic dosimetry, with combined application of MTA and lesion-based dosimetry in selected patients with advanced DTC strongly influenced the clinical decision making process, leading to change in clinical strategy in many of the cases. Careful patient selection is vital in ensuring maximum benefit for the patients undergoing personalised dosimetry.

Ethics

Ethics Committee Approval: This retrospective case series has been submitted to the National Medical Research Register (Advancing Medical Research in Malaysia) with the research ID RSCH 1D-26-01243-NC0 for ethical approval.

Informed Consent: Six patients with DTC underwent pre-therapeutic I-131 dosimetry between 2023 and 2025 after multidisciplinary team selection.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A.R., H.M.,J.,L., A.M., S.Z.A.H., H.H., Concept: N.A.R., H.M.,J.,L., S.Z.A.H., Design: N.A.R., S.Z.A.H., Data Collection or Processing: N.A.R., A.M., H.H., Analysis or Interpretation: N.A.R., A.M., H.H., Literature Search: N.A.R., Writing: N.A.R., H.M.,J.,L., A.M.

Conflict of Interest: No conflicts of interest were declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial aid.

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