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Rapid predictive dosimetry for Second Strike prescription based on whole body radioiodine kinetics in differentiated thyroid cancer

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ABSTRACT

Objective(s): In systemic radionuclide therapy such as radioiodine (I-131) for differentiated thyroid cancer, post-therapy dosimetry is essential to verify pre-therapy predictions, which in turn informs the next treatment. However, post-therapy multi-time point dosimetry is resource intensive and unfeasible in many institutions. We devised a schema of rapid predictive dosimetry by circumventing post-First Strike multi-time point dosimetry with carefully assigned gestalt values of predicted kinetics to personalise the Second Strike prescription.

Methods: Verification is performed after the First Strike. Patient-specific time-activity curve is plotted from serial measurements of whole body exposure rates to obtain its decay constant; its inverse is the whole body Time Integrated Activity Coefficient (TIAC). The percentage of whole body TIAC attributed to blood is carefully assigned by gestalt based on population kinetics tabulated in Part 1, adjusted by any metastasis on I-131 whole body scintigraphy. Marrow absorbed dose is calculated by EANM formularism. Lung safety threshold at 48h post-therapy is linearly scaled by height, where the patient's risk of lung radiotoxicity is revealed from the whole body time-activity curve value at 48h. Predictive prescription for the second I-131 fraction (Second Strike) is by careful gestalt assessment based on predicted kinetics, remaining marrow and lung tolerance, marrow dose rate constraint per fraction (0.265 Gy/h), local regulatory and facility requirements in relation to radiation protection. Tumour dosimetry is obviated under the assumption of severe tumour absorbed dose heterogeneity. The final prescription for the Second Strike is usually the lowest I-131 activity amongst all clinical, dosimetric and regulatory constraints.

Results: This schema is incorporated into a Predictive Calculator spreadsheet for rapid predictive dosimetry, and is freely available. Calculations may be completed within minutes to generate personalised predictive prescriptions, making it feasible for routine clinical implementation.

Conclusion: Our innovative schema of rapid verification and predictive dosimetry bridges the technological gap between empiric vs theranostic prescription to help institutions modernise. Its expeditious design makes this schema feasible to be integrated into the routine clinical workflow. Its predictive estimates provide invaluable dosimetric insight to inform the next I-131 fraction, allowing every prescription to be scientifically rationalised and personalised according to individual circumstances.

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Introduction

Modern theranostics involves prediction followed by verification. After the first treatment, its verification data then prospectively informs the next treatment, and the cycle of prediction-verification continues for as long as the treatment is required. In radioiodine (I-131) therapy for metastatic differentiated thyroid

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cancer, today's state-of-the-art is predictive dosimetry simulated by I-123 or I-124, endogenous or exogenous thyroid stimulating hormone (TSH) stimulation and multi-time point radiomics analyses, followed by post-therapy absorbed dose verification (1-2). This rigorous workflow represents today's pinnacle of precision medicine and should be encouraged (3). However, such advanced methods are resource intensive and beyond reach of many institutions today. Routine clinical implementation could take years, possibly decades in some developing economies. Simple averaged metrics based on Gy/MBq or MBq/kg are widely available, but are only suitable for cohort generalisations and cannot be reliably personalised to the unique circumstances of each individual patient (4).

To level the playing field, a rapid predictive prescription strategy for the First Strike was devised in Part 1 as a conceptual bridge between traditional empiric vs modern theranostic I-131 prescription (4). It is designed for under-resourced institutions that do not have access to advanced pre-therapy simulation and dosimetry, but are keen like to apply radiobiologically sound rationale to their prescription. Its key innovation is to circumvent resource intensive multi-time point dosimetry with carefully assigned gestalt values for marrow and lung kinetics based on population averages, adjusted by patient-specific clinical information (4). The First Strike schema also assumes tumour absorbed dose heterogeneity to be severe (both intra- and inter-lesional), therefore the tumour absorbed dose has no prescribed upper limit (4-5). This philosophy obviates the need for tumour predictive dosimetry, simplifying the entire prescription strategy to be constrained by the organ-at-risk, i.e., marrow or lung (4).

After the First Strike, the patient's true whole body kinetics is revealed by routine serial measurement of whole body exposure rate (μSv/h). Its I-131 whole body scintigraphy also reveals any remnants, locoregional disease or distant metastasis. Single time-point tumour dosimetry may also be performed if metastases are present (6). This workflow is conceptually regarded as a verification study to confirm pre-therapy predictions. This information, in conjunction with the likelihood of treatment response, can be projected into the future to inform the next I-131 fraction i.e., the Second Strike. The Second Strike is therefore personalised by prior knowledge of patient-specific kinetics and is no longer empiric.

Part 2 describes a rapid predictive schema for Second Strike I-131 prescription, and is a continuation of the First Strike methods described in Part 1 (4). Key dosimetric concepts such as absorbed dose heterogeneity, treatment fractions and the absorbed dose rate (Gy/h) were explained in Part 1, and is pre-requisite to understanding Part 2 (4).

Predictive Schema

Marrow: General formularism

Peripheral blood is the dosimetric surrogate for the red marrow (7). By European Association of Nuclear Medicine (EANM) formularism, the marrow absorbed dose D_M (Gy) per unit administered activity A_0 (GBq) is the sum of its beta self-irradiation and whole-body gamma contributions as (4, 7):

$$\frac{D_M}{A_0} = 61 \cdot \tau_{\text{ml of blood}} + \frac{0.106}{W} \cdot \tau_{WB}$$

(Equation 1)

Where $\tau_{\text{ml of blood}}$ is the blood Time Integrated Activity Coefficient (TIAC; previously known as Residence Time) per millilitre (h), τ_{WB} is the whole body TIAC (h), W is the patient's body weight (kg). Blood volume (ml) is estimated from the patient's height (cm) and weight (kg) using Retzlaff's formula for male and female (8).

Marrow: Absorbed dose verification

After the First Strike, routine serial measurements of whole body exposure rate (i.e., μSv/h at a fixed distance from patient) usually occur over several days, depending on institutional protocol and local regulatory requirements. Serial measurements of whole body exposure rate may be translated into whole body activities (Bq) by simple proportions, referencing to the first exposure rate measurement after oral I-131 ingestion (A_0; GBq), before voiding the bladder. Assuming mono-exponential kinetics for simplicity, a plot of the whole body time-activity curve will obtain the patient-specific whole body decay constant (λ; h^{-1}). The patient-specific whole body TIAC (τ_{WB}; h) is the inverse of its decay constant.

Based on prior work by Thomas et al. and Hanscheid et al., $\tau_{\text{ml of blood}}$ may be re-expressed in terms of τ_{WB} as (8-9):

$$\tau_{\text{ml of blood}} = \frac{f \cdot \tau_{WB}}{\text{Blood Volume}}$$

(Equation 2)

Where *f* is the fraction of τ_{WB} attributed to blood, and blood volume is in millilitres (ml).

Parameter f for the First Strike is carefully assigned by gestalt based on the presence or absence of any locoregional disease or distant metastasis seen on I-131 whole body scintigraphy, guided by population kinetics tabulated in Table 2 of Part 1 (4). Meta-analysis

in Part 1 showed that in patients prepared by recombinant human TSH (rhTSH), *f* had an overall mean value of 0.132±0.012, and in patients with metastases, *f* was 0.152±0.060 (4). The corresponding values of *f* in patients prepared with thyroid hormone withdrawal (THW) were 0.148±0.037 (overall) and 0.166±0.079 (metastases), respectively (4).

By carefully assigning a gestalt value for *f*, all parameters in Equations 1 and 2 are therefore known to solve for the marrow absorbed dose (D_M; Gy) delivered by the First Strike.

Marrow: Predicted dose rate constraint per fraction

The maximum safe I-131 marrow dose rate constraint per fraction was deduced in Part 1 to be approximately 0.265 Gy/h, where the time parameter (h) refers to the blood TIAC normalised to the administered activity (A_0; GBq) (4). In the interest of safety, this marrow dose rate may be regarded as a dosimetric constant, although in reality this constraint is expected to be slightly different in every patient. The marrow absorbed dose (D_M; Gy) per fraction constrained by marrow dose rate is therefore:

$$D_M = 0.265 \cdot (f \cdot \tau_{WB})$$

(Equation 3)

Substituting Equations 2 and 3 into Equation 1:

$$A_0 = \frac{0.265 \cdot (f \cdot \tau_{WB})}{61 \cdot \left(\frac{f \cdot \tau_{WB}}{\text{Blood volume}}\right) + \left(\frac{0.106}{W} \cdot \tau_{WB}\right)}$$

(Equation 4)

Simplified to:

$$A_0 = \frac{0.265 \cdot f}{\left(\frac{61 \cdot f}{\text{Blood volume}}\right) + \left(\frac{0.106}{W}\right)}$$

(Equation 5)

By this schema, the maximum safe A_0 (GBq) per fraction constrained by marrow dose rate is influenced by *f*, blood volume (ml) and body weight (W; kg), independent of τ_{WB} (h).

Parameter *f* in every fraction of I-131 therapy could have different values depending on how the patient's kinetics change after each fraction. For example, a patient that was revealed to have metastases on post-First Strike I-131 whole body scintigraphy can be expected to have a lower *f* value for the Second Strike if the metastases respond well to the First Strike.

To assign a gestalt predicted *f* value for the Second Strike, all available information must be carefully considered. This may include post-First Strike I-131 whole body scintigraphy findings, stimulated thyroglobulin level (and antibodies), clinical details (e.g., aggressive histopathology, intra-operative findings), other imaging modalities (e.g., ultrasound, CT, MRI, FDG PET), renal function, preparation method for the Second Strike (rhTSH vs THW) and the likelihood of response to the First Strike.

The predicted *f* value for the Second Strike is then applied into Equation 5 together with the patient's expected weight (W; kg) and blood volume (Retzlaff's formula) to obtain the predicted maximum safe A_0 (GBq) per fraction constrained by marrow dose rate.

Marrow: Predicted remaining activity tolerance

We assume the I-131 radiation tolerance of a treatment naïve marrow to be 2 Gy cumulatively (7). If the patient has pre-existing haematologic pathology, Full Blood Count or peripheral blood film abnormalities, then the marrow tolerance should be adjusted by clinical gestalt to a value below 2 Gy. The marrow absorbed dose delivered by the First Strike was already calculated from Equations 1 and 2. The patient's remaining marrow tolerance (Gy) for the Second Strike is therefore:

$$D_{Second\ Strike} = 2 - D_{First\ Strike}$$

(Equation 6)

The Second Strike predicted *f* value for Equations 2 and 3 was already assigned in the previous section. To fully solve Equations 1, 2 and 3 for the Second Strike, a gestalt value for predicted τ_{WB} (h) must also be carefully assigned in a similar manner as predicted *f*.

Crucially, the gestalt assignment of a predicted τ_{WB} value for the Second Strike is guided by the measured First Strike whole body TIAC, and therefore not empiric. Finally, Equation 6 is applied into Equation 1 to calculate the patient's predicted remaining marrow I-131 activity tolerance (A_0; GBq) for the Second Strike.

Lung: Activity constraint and verification

In patients with diffuse lung metastases, guidelines recommend a retained whole body I-131 activity of <2.96 GBq at 48 hours to avoid serious lung radiotoxicity, based on early observations by Benua et al (7, 10).

Conceptually, the retained whole body I-131 activity at 48h reflects the dose rate (Gy/h), although this parameter is indirectly inferred and not explicitly calculated (4,11).

Our schema linearly scales the "whole body 2.96 GBq at 48 h" lung constraint based on the Standard Female of height 163 cm, not weight, explained in Part 1 (4). The adjusted patient-specific lung constraint (GBq) at 48 h is therefore:

$$A_{Lung\ constraint} = \left(\frac{Height}{163}\right) \cdot 2.96$$

(Equation 7)

Where height is expressed in cm and 2.96 GBq is the constraint of whole body I-131 activity retained at 48 h.

After the First Strike, verification of lung safety is simply the 48 h value of the measured whole body time-activity curve (GBq). This immediately reveals whether the patient is at risk of any significant lung radiotoxicity.

Lung: Predicted remaining activity tolerance

After the First Strike, the patient's remaining lung activity tolerance (GBq) at 48 h post-administration is:

$$A_{Second\ Strike} = A_{Lung\ constraint} - A_{First\ Strike}$$

(Equation 8)

Where, $A_{First\ Strike}$, $A_{Second\ Strike}$ and $A_{Lung\ Constraint}$ all refer to whole body I-131 activities (GBq) retained at 48 h.

The predicted whole body decay constant (λ_{WB} ; h^{-1}) for the Second Strike is the inverse of the predicted whole body TIAC (i.e., τ_{WB}) that was assigned during marrow predictive dosimetry. The Second Strike I-131 prescription (A_0 ; GBq) constrained by the predicted remaining lung tolerance is therefore:

$$A_0 = \frac{A_{Second\ Strike}}{e^{-\lambda_{WB} \cdot 48}}$$

(Equation 9)

For multiple subsequent I-131 fractions, the simple sum of whole body activities at 48h for each fraction indirectly reflects the cumulative lung dose. This summed value may be applied into Equation 8 to derive the remaining lung tolerance.

Predictive calculator

Our schema is incorporated into a Predictive Calculator spreadsheet for rapid predictive dosimetry, freely provided in Supplemental Data. Predictive calculations may be completed within minutes to generate personalised prescriptions, making it feasible for routine implementation into any busy theranostics clinic. Our Predictive Calculator is designed to sum the cumulative marrow and lung doses up to five I-131 fractions, to inform up to the sixth fraction.

Interpretation of the suggested prescriptions generated by our Predictive Calculator requires careful multi-faceted consideration of the organ-at-risk (marrow vs lung), absorbed dose and dose rate constraints, local regulatory, facility and protocol requirements in relation to radiation protection. The final I-131 prescription is usually the lowest activity amongst all considerations. This Predictive Calculator has been clinically implemented into our routine post-therapy workflow for several years. It has provided us with invaluable predictive insight to guide personalised therapy planning and informed consent.

A worked example of post-First Strike verification and predictive prescription for the Second Strike is provided in Figures 1 and 2, presented in full detail in Supplemental Data. This clinical example illustrates how our predictive schema helps to define the marrow and lung tolerance limits in a metastatic patient of small body habitus, and how it's personalised predictive estimates impact future therapy planning.

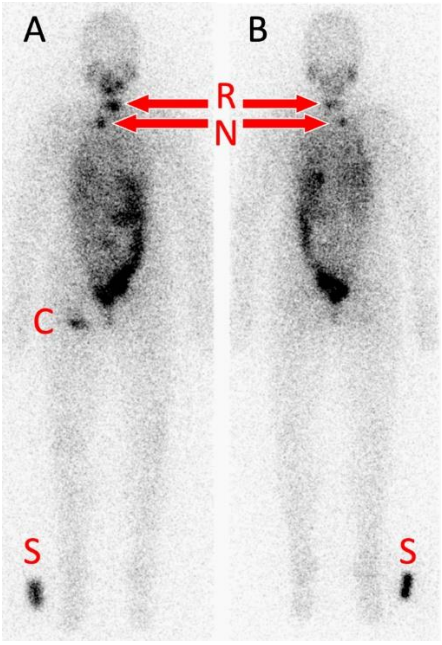

Figure 1. 20-year-old female with T1a N1b right multi-focal papillary thyroid carcinoma and multiple right-central cervical nodal metastases with extra-nodal extension. Surgically treated with total thyroidectomy with right central and right lateral neck dissection. Whole body I-131 scintigraphy was performed 6 days after her first I-131 fraction using oral 3.76 GBq prepared by THW. TSH 86 mU/L, thyroglobulin 44 ug/L, negative anti-thyroglobulin. Scintigraphy in anterior (**A**) and posterior (**B**) views show a thyroid remnant (**R**), a I-131 avid right lower cervical nodal metastasis (**N**) and I-131 avid diffuse lung metastases. Right groin activity is due to urine contamination on clothing (**C**). A syringe (**S**) of known I-131 activity is placed adjacent to the feet to facilitate dosimetry

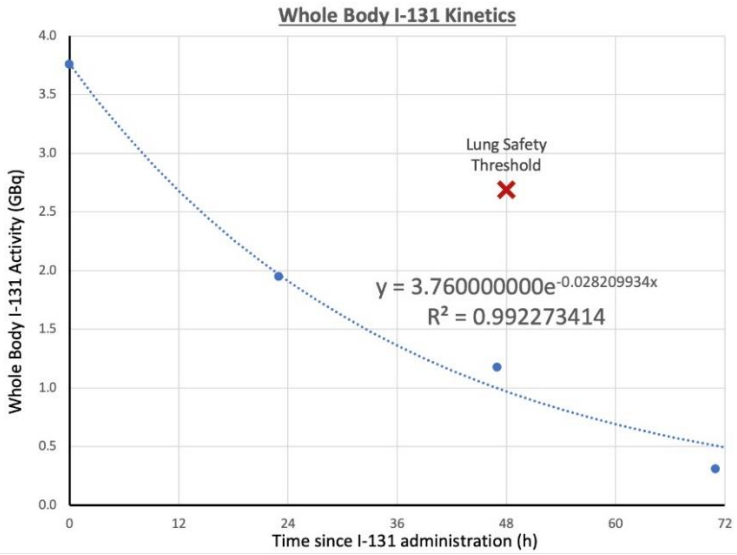

Figure 2. Continued from Figure 1. This patient is much smaller than the average female, measuring only 148cm tall and weighing only 43 kg. She therefore falls far beyond average population norms; hence typical assumptions are hazardous for her. Her serial I-131 whole body exposure rate was plotted into a mono-exponential time-activity curve to obtain its patient-specific decay constant (λ; h^{-1}). Her lung tolerance scaled by height is 2.7 GBq at 48 h (X). The time-activity curve immediately reveals that she will not experience any significant lung radiotoxicity. Due to her unfavourable combination of low blood volume (small body habitus) and prolonged whole body TIAC, her marrow absorbed dose was estimated to be 0.835 Gy of the 2 Gy cumulative limit. After carefully assigning gestalt predicted values to the future second fraction's whole body TIAC (28 h) and percentage of TIAC attributed to blood (15%), her remaining marrow tolerance was estimated to be only 6.9 GBq, where 6.59 GBq may be prescribed constrained by marrow dose rate per fraction. Her predicted remaining lung tolerance is 9.53 GBq. This predictive knowledge informs the treating team that her limiting organ is her marrow, not lung, despite having diffuse lung metastases, and that her remaining marrow tolerance is low. Given her young age, her future I-131 therapies must be carefully deliberated and timed with appropriately long inter-fraction intervals to mitigate her risk of marrow toxicity, in conjunction with haematologic surveillance. Her full predictive dosimetry is presented in Supplemental Data

Discussion

The traditional practice of empiric prescription for systemic radionuclide therapy is an outdated concept that was acceptable in the early years of its conception, but today, more than half a century later, now scientifically obsolete (4-5, 12). The archaic nature of empiric prescription lacks radiobiologic rationale and is therefore inappropriate for modern personalised oncology (4-5, 12). Despite its flaws, the continued widespread practice of empiric prescription today is partly explained by its deeply entrenched culture through generations of Nuclear Medicine specialists (4-5, 12). As a result, the basic question "what absorbed dose is being prescribed?" still draws a blank in most tertiary institutions today. The Nuclear Medicine fraternity must urgently evolve to modernise our practice of systemic radionuclide therapy, especially in the setting of inoperable metastatic disease (3-5, 12).

Our rapid predictive schema for the First and Second Strikes will empower any institution with the capability to radiobiologically rationalise I-131 prescriptions according to each patient's unique circumstances (4). It conceptually circumvents the rigorous workflow of multi-time point dosimetry by replacing it with carefully assigned values of I-131 kinetics based on population averages, adjusted by clinical gestalt (4). Our predictive schema may be regarded as an interim measure to help bridge the technical gap between empiric vs theranostic prescription, while awaiting full transition to modern personalised predictive dosimetry (4). The general principles of this schema may be applied to any form of pre-therapy simulation (e.g., I-123, I-124, very low activity I-131), with additional considerations for dosimetric uncertainty.

Conclusion

We have devised innovative schemas for rapid I-131 predictive dosimetry for the First and Second Strikes (4). These schemas have been incorporated into freely available Predictive Calculators that can be completed within minutes, and are therefore feasible to be

implemented into the routine workflows of any busy theranostics clinic. Its predictive estimates provide invaluable dosimetric insight to inform the next treatment. This allows the next prescription to be scientifically rationalised and personalised according to individual circumstances, down to a single becquerel. Yes, the Holy Gray exists. Learn from modern radioembolization (5).

Declarations

Ethics approval and consent to participate: This work was approved by our institutional review board (QA2021112) with waiver of consent.

Consent for publication

The author Y.H. Kao consents to this publication.

Availability of data and material

All data and materials are available to the reader.

Competing interests

Y.H. Kao previously received research funding from Genzyme Corporation and Sirtex Medical Limited, and is a consultant for Sirtex Medical Limited.

Financial and conflict of interest disclosure

This work is unfunded. Y.H. Kao previously received research funding from Genzyme Corporation and Sirtex Medical Limited, and is a proctor for Sirtex Medical Limited.

Authors' contributions

Y.H. Kao conceived, researched and wrote this entire work.

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