Adjustment of the iodine ICRP population pharmacokinetic model for the use in thyroid cancer patients after thyroidectomy

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Abstract

Introduction: Biokinetic models developed for healthy humans are not appropriate to describe biokinetics in thyroid cancer patients following thyroidectomy. The aim of this study was to adjust the population model for iodine proposed by the International Commission on Radiological Protection (ICRP) for the use in these patients.

Method: Rate constants of the ICRP publication 128 model for iodine were adjusted using the population modelling software package Monolix to describe activity retention in whole-body, thyroid, blood and protein-bound iodine observed in 23 patients. The new set of rate constants was compared to the four uptake scenarios proposed in ICRP publication 128.

Results: Flow from the inorganic iodide in blood compartment into the first thyroid compartment decreases to 0.15 day^{-1} compared to a value of 7.27 day^{-1} for the ICRP publication 128 model with a medium uptake. The transfer from first to second thyroid compartments and the outflow from the second thyroid compartment increases. An increased turnover rate of extrathyroidal organic iodine is observed. The rate constant from inorganic iodide in blood to kidney was also adjusted. Overall a good agreement was found between the adjusted model and the activity retention in thyroid cancer patients.

Conclusions: The adjustment of population pharmacokinetic models to describe the biokinetic properties of specific patient populations for therapeutic radiopharmaceuticals is essential to capture the changes in biokinetics. The proposed set of rate constants for the established ICRP publication 128 model can be used to more accurately assess radiation protection requirements for the treatment of thyroid cancer patients using radioiodine.

Keywords

Radioiodine, biokinetic model, population model, thyroid cancer

Introduction

The International Commission on Radiological Protection (ICRP) has published biokinetic models for many commonly used radiopharmaceuticals (1). These models have been used to calculate dose coefficients for administration of radionuclides to patients. For patients undergoing diagnostic examinations in nuclear medicine, absorbed doses to organs and tissues are often calculated following the Committee on Medical Internal Radiation Dose (MIRD) formalism (2) using dosimetric models with human computational phantoms and the respective radiopharmaceutical biokinetic model (3). ICRP models are employed to assess radiation protection requirements for patients in the nuclear medicine (NM) and molecular radiotherapy (MRT) settings, and to provide radiation protection guidance to staff, patients and caregivers (4-6).

A biokinetic model incorporating normal thyroid function (1, 7, 8) is not appropriate to describe the use of radioiodine to treat residual tissue following partial or total thyroidectomy in thyroid cancer patients. The biokinetics in these patients are significantly affected by partial or total removal of the thyroid gland and the use of recombinant thyroid-stimulating hormone (rhTSH) or thyroid hormone withdrawal (THW) (9). Excretion of radioiodine from the body is often faster. ICRP publication 128 (ICRP128) provides iodine biokinetics for blocked, low, medium and high thyroid function. No rate constants are provided in ICRP128 for patients following thyroidectomy and activity retention in the thyroid remnant cannot be described with the scenarios considered in ICRP128 (1).

Population pharmacokinetic modelling is used to study a substance's absorption, distribution, metabolism, and excretion in a population of interest, such as a population with a specific pathology. Population pharmacokinetic modelling using non-linear mixed effects (NLME) allows for inter-patient variability by including both fixed and random effects (10). Simplistic biokinetic models have been created using NLME for specific MRT patient cohorts (11-13),

61 although more complex models are required to include major organs for radiation protection
62 purposes.

63 A set of rate constants for the established ICRP128 biokinetic model was developed here for
64 radioiodine treatment of thyroid cancer following thyroidectomy. The rate constants of the
65 ICRP128 population biokinetic model were adapted using NLME to describe the
66 pharmacokinetics of radioiodine in a thyroid cancer patient cohort based on actual patient
67 data. These were compared to radioiodine pharmacokinetics in healthy individuals
68 represented by the established ICRP models.

69 Method

70 ***Radioiodine therapy patient data***

71 Thyroid remnant, whole-body and blood activity retention data were taken from a study by
72 Flux et al (14). 23 patients, 15 female and 8 male, were administered with a nominal activity
73 of 3000 MBq of ^{131}I-NaI. Patients were either not given thyroid hormone replacement between
74 surgery and ablation or thyroid hormones were discontinued for 14 days prior to radioiodine
75 treatment. No rhTSH was used in this study. The median age of patients was 41 years (range
76 18-70 years). Only patients with near-total or complete thyroidectomy were included in the
77 study. Furthermore, patients were excluded from the study if: they had distant metastases at
78 presentation, were treated with external beam radiotherapy or had been administered with
79 iodine-containing contrast, ^{123}I or ^{131}I tracers in the three preceding months before
80 administration of the therapeutic dose of ^{131}I.

81 Activity retention in the thyroid remnant was obtained from a minimum of three SPECT
82 acquisitions covering the neck and superior mediastinum using a Philips Forte gamma
83 camera. Scans were performed at nominally 24, 48 and 72 hours post administration. Two
84 patients had an additional scan at 96 hours and one patient had an additional scan at 32 hours.
85 Triple-energy-window scatter correction was used (15).

Blood samples were taken at 24, 48, 72 and 144 hours post administration. Protein bound iodine (PBI) was extracted from blood. The major constituents of PBI are the thyroid hormones, triiodothyronine (T3) and thyroxine (T4) (16, 17). Activity concentration of iodide and PBI in blood were determined and converted to total activity in blood with the assumption of a total blood volume of 5300 ml for adult males and 3900 ml for adult females (18). Whole-body retention measurements were performed directly after administration (baseline value) and at regular intervals until discharge of the patient.

All activity retention measurements were decay corrected back to the time of administration. Further details about data acquisition and processing are provided in Flux et al (14).

Model adjustment

Monolix 2019R2 (Antony, France: Lixoft SAS, 2019) was used for NLME modelling. The structural base model of ICRP128, including the human alimentary tract model from ICRP publication 100 (ICRP100) (19), was implemented as shown in Figure 1. A combined error model was chosen for the residual errors with a log-normal residual error distribution (20). Fitted rate constant distributions were assumed to be log-normally distributed to ensure positivity of the values on all parameters. The ICRP128 model with the medium uptake rate constants in the thyroid was used as a base model.

The iodine biokinetics in this patient cohort may differ from a healthy euthyroid population for several reasons. Patients have undergone thyroidectomy and, as a result of THW, become hypothyroid and have increased thyroid stimulating hormone (TSH) levels which regulate sodium iodide symporter (NIS) expression in thyroid tissue (21).

The trapping rate of iodide into thyroid from blood depends in part on thyroid blood flow and NIS expression. This process is described in the model by the rate constant from Blood 1 to Thyroid 1. The altered blood supply to the thyroid remnant following thyroidectomy and increased NIS expression resulting from high TSH (21) should affect the rate of iodide trapping.

Several stages of organification of iodide to thyroid hormone are upregulated by increased TSH levels (21-23). Additionally, Robertson et al found an increased organification rate in thyrotoxic patients compared to euthyroid patients (22). Therefore, a change in the rate constant from Thyroid 1 to Thyroid 2 may also be expected given the hypothyroid condition of thyroid cancer patients under THW and increased TSH levels. The rate of secretion of thyroid hormone (T3 and T4) from thyroid to blood, which is described by the rate constants from Thyroid 2 to Blood 2, increases with TSH (8, 24).

Reductions in glomerular filtration rate (GFR) (25, 26), tubular secretion and re-absorption (26) in hypothyroid patients have been reported. Duranton et al measured increased serum creatinine in patients under THW (27). Excretion of iodide by glomerular filtration is accounted for by the rate constant from Blood 1 to Urinary bladder contents.

The ratio of T3 to T4 is elevated with rising TSH levels (24, 28-31). This is expected to result in an increased turnover rate of extrathyroidal organic iodine due to the higher turnover rate of T3 compared to T4 (32, 33). The turnover of extrathyroidal organic iodine is represented by three rate constants, namely Kidney 2 to Blood 1, Liver 2 to Blood 1 and Other 4 to Blood 1. The turnover is assumed to occur at the same rate from all three compartments (8).

The seven rate constants described above and indicated in red in Figure 1 were allowed to vary in the fitting to the thyroid cancer patient data set. We could find no further evidence in literature to support the adjustment of any of the remaining rate constants from the values published in ICRP100 and ICRP128. It should be noted that in the current model voiding was modelled as a constant excretion (8) which differs from the excretion model proposed by ICRP.

In the fit process, compartmental model rate constants were varied iteratively to achieve the best agreement between activity retention observed in patients and predictions by the compartmental model. For this purpose, thyroid activity retention in patients was taken to be the sum of thyroid compartments 1 and 2 in the model. Furthermore, patient whole-body activity retention was taken to be the sum of all compartments in the model excluding faeces

and urine. The blood and PBI activity retention data were assumed to correspond to Blood 1 and Blood 2 compartments, respectively, with Blood 1 being the inorganic iodide and Blood 2 the organic iodine in blood.

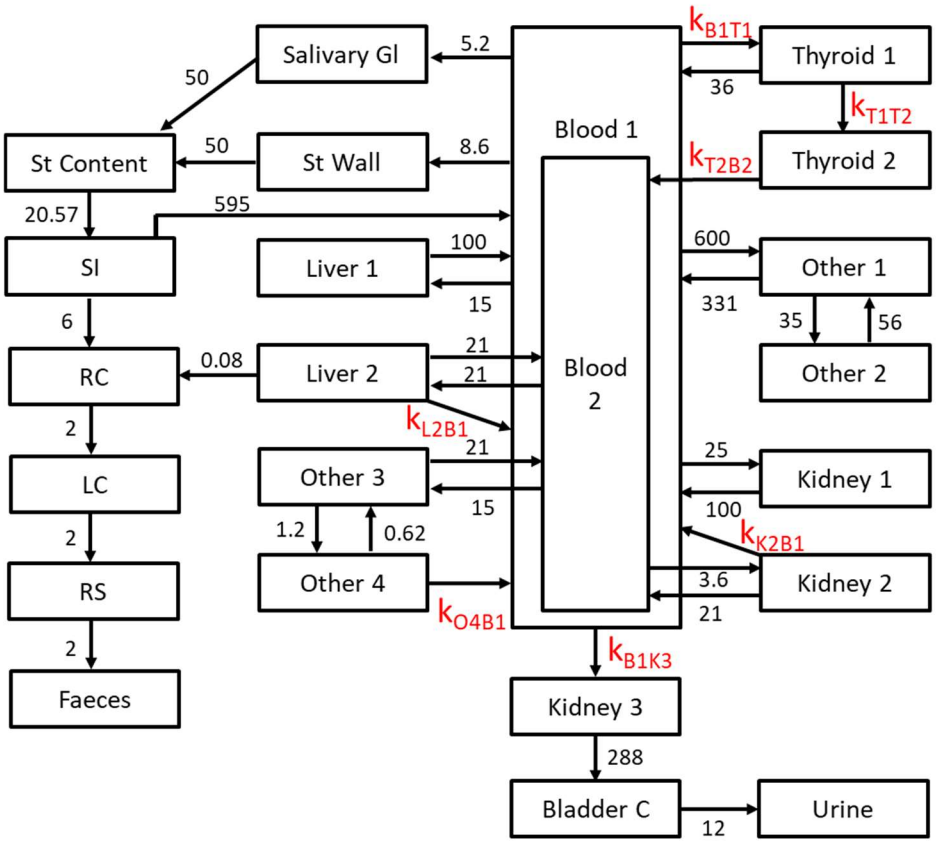

Figure 1: The structural base model implemented in Monolix. Rate constants shown in red were tested during the model building process. In the base model, Blood 1 is the inorganic iodide in blood, Blood 2 is the organic iodine in blood, Thyroid 1 is the inorganic iodide in the thyroid, Thyroid 2 is the organic iodine in the thyroid, Kidney 1 is the inorganic iodide in kidneys, Kidney 2 is the organic iodine in kidneys, and Liver 1 is the inorganic iodide in liver, Liver 2 is the organic iodine in liver. Other 1 to Other 4 represent any tissues not specifically included in the model. Salivary Gl are the salivary glands, St Wall is the stomach wall, St Contents are the stomach contents, SI are the small intestines, RC is the right-sided colon, LC is the left sided colon, RS is the rectosigmoid, Kidney 3 is an additional kidney compartment in the ICRP128 model representing transfer to the bladder and Bladder C are the bladder contents. All rate constants are in units of day^{-1}.

Model comparison to ICRP128

Model predictions of the final population model were compared to individual observations in patients. The biological retention predictions in each compartment of the final population model were compared to the predictions of the ICRP128 base model.

Results

Model adjustment

Rate constants of the updated ICRP128 population model developed here are presented in Table 1 and compared to the respective rate constants of the ICRP128 base model. Flow from the inorganic iodide in blood compartment (Blood 1) into the first thyroid compartment (Thyroid 1) decreases, the rate constant from inorganic iodide in thyroid (Thyroid 1) to organic iodine in thyroid (Thyroid 2) approximately doubles and outflow from the second thyroid compartment (Thyroid 2) increases by two orders of magnitude. Transfer from inorganic iodide in blood (Blood 1) to Kidney 3 is found to be lower than in the ICRP128 model. The turnover rate of extrathyroidal organic iodine, represented by the three rate constants from Kidney 2, Liver 2 and Other 4 to inorganic iodide in blood (Blood 1), is estimated to increase from 0.14 day^{-1} to 0.29 day^{-1}.

Table 1: Comparison of rate constants of the ICRP128 base model and the adjusted rate constants for the model developed here.

Rate constant	Flow between compartments (see Figure 1)	ICRP128 (medium uptake) [day^{-1}]	This model [day^{-1}]
k_{B1T1}	Blood 1 → Thyroid 1	7.27	0.15
K_{T1T2}	Thyroid 1 → Thyroid 2	95	181
k_{T2B2}	Thyroid 2 → Blood 2	0.0077	0.50
k_{B1K3}	Blood 1 → Kidney 3	11.83	6.87
k_{K2B1}, k_{L2B1}, k_{O4B1}	Kidney 2 → Blood 1, Liver 2 → Blood 1, Other 4 → Blood 1	0.14	0.29

Figure 2 shows the predictions of the thyroid cancer patient model, compared to the predictions of the ICRP128 base model for the different uptake scenarios considered and the observed activity retention in patients. Predicted and measured activity retention in compartments has been corrected for physical decay. A good agreement was found between the predictions of the model and the activity retention measured in patients.

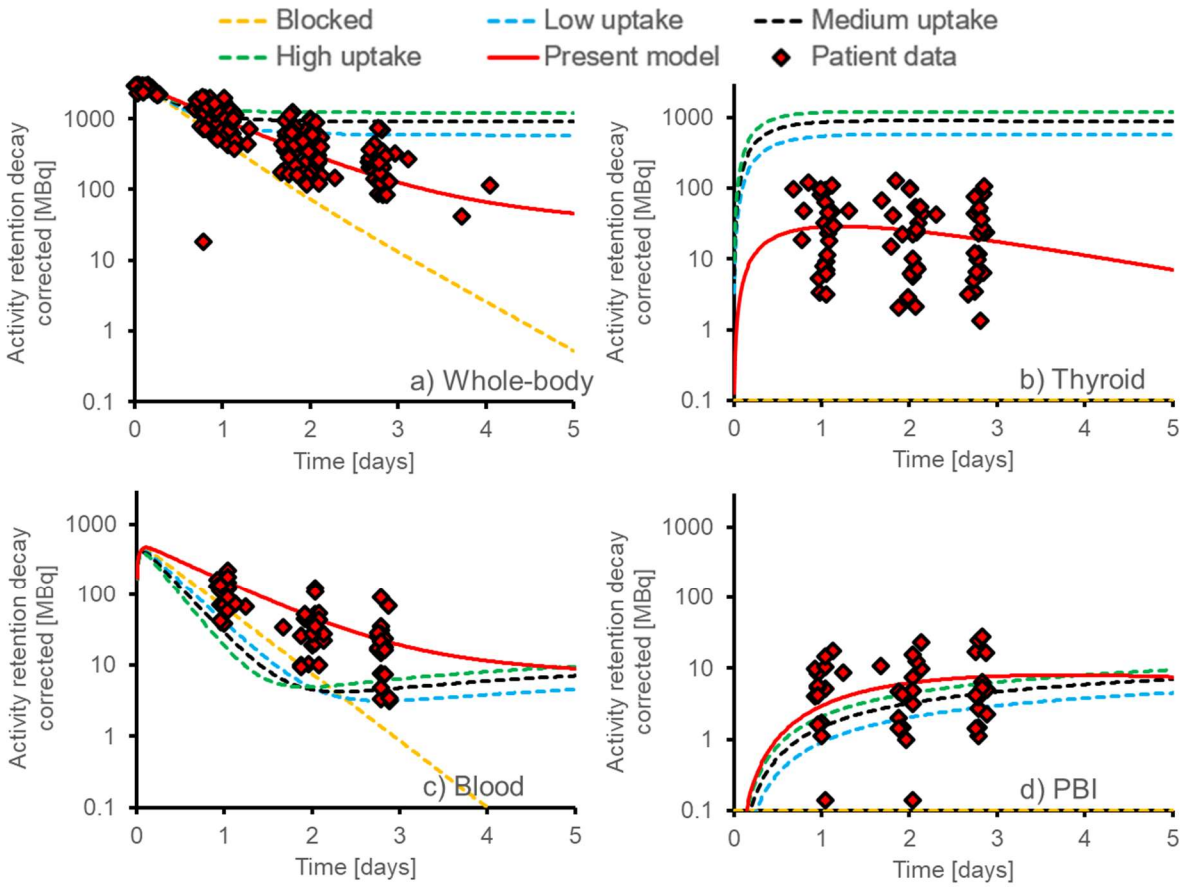

Figure 2: Comparison of predictions of the final population model for thyroid cancer patients administered with 3000 MBq of ^{131}I-NaI (red solid line) obtained from a fit of rate constants k_{B1T1}, k_{T1T2}, k_{T2B2}, k_{B1K3}, k_{K2B1}, k_{L2B1} and k_{O4B1}, of the ICRP128 base model, to patient data of Flux et al (14) (red diamonds). The predictions of the ICRP128 model for blocked thyroid (yellow dashed line), low (blue dashed line), medium (black dashed line) and high (green dashed line) uptake are presented for comparison. Activity retention was decay corrected back to the administration time and, therefore, biological retention is presented excluding physical decay.

Model comparison to ICRP128

Population model predictions were compared to the observed values in the 23 patients (Figure 2 and Figure 3). Predicted and observed whole-body and blood retentions are in good agreement, while the population model appears to perform less well to predict the variability in uptake in the thyroid remnant and PBI.

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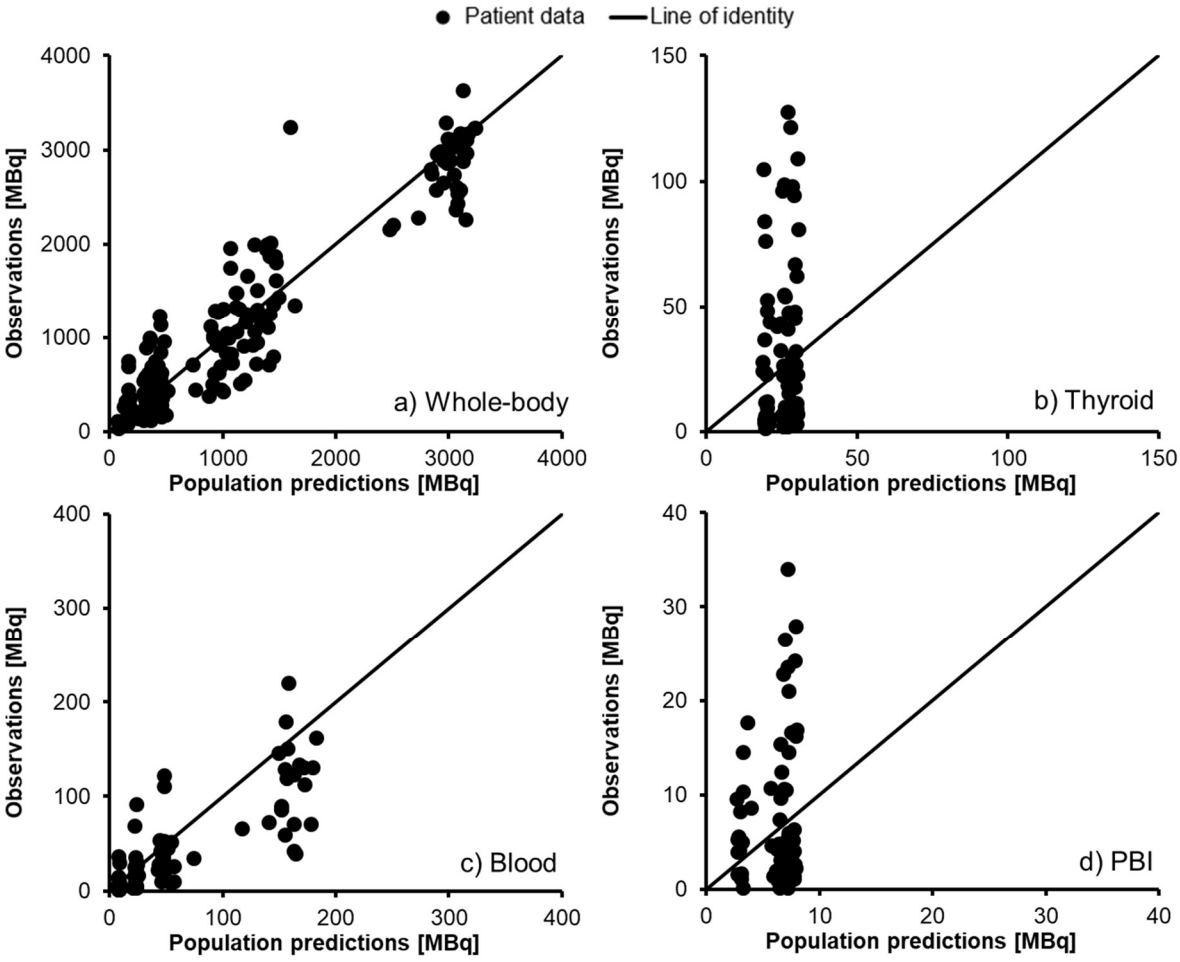

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198 **Figure 3: Comparison of population model predictions to observations in patients for activity retention in**
199 **(a) whole-body, (b) thyroid remnant, (c) blood and (d) PBI after a 3000 MBq ^{131}I-NaI administration.**

200 As shown in Figure 2, the model with rate constants to describe a post-thyroidectomy thyroid
201 cancer patient population shows a slower clearance from blood compared to ICRP128 while
202 whole-body excretion is faster than the low, medium and high uptake scenarios in the
203 ICRP128 model and slower than the blocked thyroid scenario. Thyroid activity retention peaks
204 at 1.0% of the administered activity, which is markedly lower, compared to the low, medium
205 and high uptake scenarios of ICRP128 of approximately 19%, 30% and 40% uptake in the
206 thyroid. Maximum uptake in the thyroid remnant is predicted to occur around 29 hours, which
207 is slightly faster than for the low, medium and high uptake scenarios of ICRP128 where peak
208 uptake is observed between 42 to 54 hours after administration.

Discussion

Results presented here highlight the necessity of adjusting population pharmacokinetic models to describe the biokinetic properties of specific patient populations for therapeutic radiopharmaceuticals. Current ICRP models have been developed based on data from healthy human or animal studies although biokinetic properties may change for patient populations undergoing treatment. It has been shown here that the development of a patient-specific population biokinetic model is feasible even with a limited number of patients and measurements per patient.

The markedly faster urinary excretion predicted from this model, which has also been observed in previous studies (34, 35), is an important factor in the MRT setting as it will affect radiation protection guidance provided to staff, patients and caregivers. The model proposed here with lower iodine uptake in the thyroid and faster urinary excretion compared to ICRP128, provides a more accurate estimate of activity retention in this patient cohort. This could inform radiation protection restrictions based on relevant national legislative requirements.

The observed increased rates of organification of iodide and secretion of thyroid hormones are in agreement with literature evidence due to the high TSH caused by THW (21-24, 36). In addition, the expected increase in turnover rate of extrathyroidal organic iodine identified from literature (32, 33) was confirmed in the present model. Also in agreement with literature (25-27), the excretion of iodide by glomerular filtration decreased.

A patient-specific pharmacokinetic model for dose assessment following radionuclide therapy may require rate constants to be derived from either patient-specific covariates as part of a physiologically-based pharmacokinetic (PBPK) model (37), or by adjustment of models to patient-specific activity retention measurements (38). No patient-specific covariates were added during the model development due to the small number of patients included in this retrospective analysis. Inter-individual random effects, therefore, remain unexplained in the current model. In the current state, the model is not able to make accurate predictions of

individual patient biokinetics, especially for activity retention in the thyroid remnant, as demonstrated by Figure 3. EANM, EFOMP, EFRS, ESR and ESTRO have published a common strategic research agenda for radiation protection in medicine (39), which includes the refinement, validation and implementation of new biokinetic models for dosimetry in MRT. A prospective study following a defined population modelling plan as defined in current best-practice guidelines (40) should be performed to develop a more accurate model that could potentially be used for individual patient biokinetic predictions which would enable individualised radiation protection restrictions and could be used in the dose assessment. The model presented here will be validated and extended using activity retention data and covariates for 100 patients collected as part of a concurrent series of non-randomised, non-blinded, prospective observational studies at four centres (Royal Marsden Hospital, Universitätsklinikum Marburg, Universitätsklinikum Würzburg and Institute Universitaire du Cancer de Toulouse Oncopole) as part of MEDIRAD Work Package 3 (41, 42).

Limitations of the current study include the relatively small patient sample and the fact that data were only available for patients administered with a fixed activity of 3000 MBq, and without rhTSH stimulation. Hänscheid et al (35) have shown that the effective half-time in remnant thyroid tissue varies based on the patient preparation prior to radioiodine therapy, namely rhTSH stimulation or THW. Furthermore, Ito et al presented results that the T3/T4 ratio is lower in patients with total thyroidectomy during levothyroxine therapy when compared to control (31). Therefore, a further model might be required for the sub-population of patients administered under rhTSH stimulation. The model should also be validated for varying amounts of administered activities. Nevertheless, the model has proven to accurately describe the patient biokinetics for the patient cohort presented here.

Conclusions

A set of rate constants was developed for the established ICRP128 model to accurately describe biokinetics of a thyroid cancer patient population with THW. The model developed

here can be used to more accurately assess radiation protection requirements for the treatment of thyroid cancer patients using radioiodine.

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Ethical statement

Ethics committee approval and informed consent from all patients was obtained.

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