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GUIDELINES

# EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases

**Heribert Hänscheid · Cristina Canzi · Wolfgang Eschner · Glenn Flux · Markus Luster · Lidia Strigari · Michael Lassmann**

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**Abstract** The EANM Dosimetry Committee Series "Standard Operational Procedures for Pre-Therapeutic Dosimetry" (SOP) provides advice to scientists and clinicians on how to perform patient-specific absorbed dose assessments. This particular SOP describes how to tailor the therapeutic activity to be administered for radioiodine therapy of benign thyroid diseases such as Graves' disease or hyperthyroidism. Pretherapeutic dosimetry is based on the assessment of the individual $^{131}$I kinetics in the target tissue after the administration of a tracer activity. The present SOP makes proposals on the equipment to be used and guides the user through the measurements. Time schedules for the measurement of the fractional $^{131}$I uptake in the diseased tissue are recommended and it is shown how to calculate from these datasets the therapeutic activity necessary to administer a predefined target dose in the subsequent therapy. Potential sources of error are pointed out and the inherent uncertainties of the procedures depending on the number of measurements are discussed. The theoretical background and the derivation of the listed equations from compartment models of the iodine kinetics are explained in a supplementary file published online only.

**Keywords** Dosimetry · Radioiodine therapy · Benign thyroid disease

G. Flux, L. Strigari and M. Lassmann are members of the EANM Dosimetry Committee; W. Eschner is a member of the EANM Physics Committee; and M. Luster is a member of the EANM Therapy Committee.

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H. Hänscheid · M. Lassmann (✉)
Department of Nuclear Medicine, University of Würzburg,
Oberdürrbacher Str. 6,
97080 Würzburg, Germany
e-mail: Lassmann_M@klinik.uni-wuerzburg.de

C. Canzi
Department of Nuclear Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

W. Eschner
Department of Nuclear Medicine, University of Cologne, Cologne, Germany

G. Flux
Joint Department of Physics, Royal Marsden NHS Foundation Trust & Institute of Cancer Research, Sutton, UK

M. Luster
Department of Nuclear Medicine, University of Ulm, Ulm, Germany

L. Strigari
Laboratory of Medical Physics and Expert Systems, National Cancer Institute Regina Elena, Rome, Italy

## Introduction

This paper is the second in a series of disease-specific and patient-specific "how-to" procedure guidelines. The purpose of this EANM Dosimetry Committee Series "Standard Operational Procedures for Pre-Therapeutic Dosimetry" (SOP) is to provide recommendations to scientists and clinicians on how to perform pretherapeutic patient-specific absorbed dose assessments thus adding supplementary and comprehensive

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information to the corresponding medically oriented disease-specific guidelines provided by the Therapy Committee of the EANM.

The main objective of radioiodine ($^{131}$I) therapy of benign thyroid diseases is the treatment for hyperthyroidism as observed in Graves' disease or toxic adenoma aiming at euthyroidism or, in an ablative concept for Graves' disease, at hypothyroidism recompensated by thyroxin medication. Patients with a large nontoxic goitre who are most often diagnosed in regions with dietary iodine deficiency might be treated to reduce the thyroid volume with preserved thyroid function [1].

The rationale behind dosimetry prior to therapy is to determine the $^{131}$I activity that is most likely to lead to therapeutic success but that limits the radiation exposure to the amount necessary. Such an approach is mandated by the Council Directive 97/43/Euratom [2] which requires that "for all medical exposure of individuals for radiotherapeutic purposes, … exposures of target volumes shall be individually planned; taking into account that doses of non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure." Implementation of dosimetry prior to therapy varies among the different European nations; while it is mandatory in some countries it remains exceptional in others. Although the administration of fixed activities is still covered by the actual EANM procedure guideline for therapy of benign thyroid disease [1], there is increasing evidence that "personalised" and "evidence-based" treatments could improve the quality and outcome of radionuclide therapy [3]. Usually empirically determined values for the absorbed dose in the diseased tissue are targeted. The corresponding recommendations of the medical guideline [1] should be followed. For example, 300–400 Gy absorbed dose should be used to ablate autonomous nodules, and in patients with Graves' disease, the thyroid absorbed dose should be 150 Gy if aiming at euthyroidism or 200–300 Gy for ablation.

This SOP provides recommendations on how to tailor the therapeutic activity such that the absorbed dose to the thyroid or diseased parts of the thyroid yields the prescribed value. It is applicable if a low activity of $^{131}$I is administered pretherapeutically followed by measurements of the fractional uptake in the target tissue with a dedicated probe or by planar scintigraphy. Tomographic imaging with PET or SPECT with or without X-ray CT is not specified in this SOP, but may be an option for performing dosimetry after standardized procedures have been established and validated. Although it is not considered to be a complete dosimetry, the procedure for calculating the therapeutic activity from a single uptake measurement 1 or 2 days after the administration of a tracer activity is described in the guideline; however, general use of the method as well as administration of fixed activities or activity dosing linearly to the target mass and to the targeted absorbed dose is not recommended. A derivation of the formulas recommended for determining the therapeutic activity as well as a worked example of a pretherapeutic dosimetry can be found in the Electronic supplementary material.

The EANM Dosimetry Committee guidance document on good practice of clinical dosimetry reporting should be consulted [4] for the documentation of the procedures. The intention of this SOP was not to provide a discussion of the medical background of the procedure or the target absorbed doses to be administered for effective therapy. For detailed information on these aspects as well as particulars on indications, patient preparation and precautions, the reader is referred to the corresponding medical guideline [1].

## Equipment

### Thyroid neck phantom

The use of a phantom mimicking a thyroid in a neck (e.g. a thyroid uptake neck phantom according to specifications by IAEA or ANSI) is recommended to determine the sensitivity of the measuring device during in-vivo assessments, i.e. the count rate per activity in a typical target tissue (Fig. 1). For a realistic representation, the phantom material should have radiation absorption and scatter characteristics similar to those of human soft tissue, and the calibration depth (i.e.

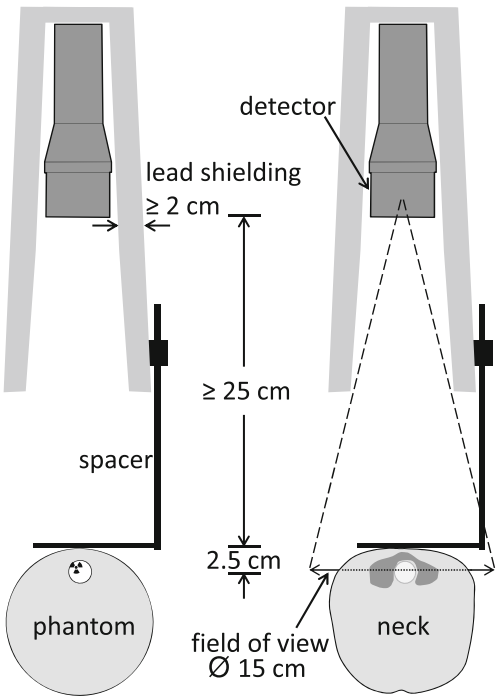


**Fig. 1** Probe measurements of a phantom and a neck with identical geometry

the mean depth of the activity distribution under the surface) should be about 2 to 2.5 cm.

If a dedicated phantom is not available and cannot be purchased, the device should be calibrated by measuring the activity standard through a 2-cm thick plastic plate, e.g. Lucite. The surface of the plate must have the same distance to the detector as the neck surface in patient assessments and the activity standard must be as close as possible to the opposite side of the plate to adequately mimic both attenuation depth and distance of a typical target tissue.

The tracer activity to be used for the pretherapy dosimetry should be measured in the phantom prior to the administration. The resulting count rate value represents 100 % uptake and the count rate divided by the activity can be used as a constancy check for the sensitivity of the device. Alternatively, the tracer activity can initially be measured at a fixed distance in free air. In this case, the count rate must be corrected by a calibration factor accounting for the differences in the sensitivities in activity measurements in the phantom and in free air to represent 100 % uptake in typical target tissue.

## Probe

### *Detector and shielding*

A sodium iodide crystal of 5 cm diameter and 5 cm depth (2×2 inches) is most often used and is recommended as the detector in dedicated shielded probes for $^{131}$I uptake measurements. This offers a reasonable compromise among sufficient sensitivity, low expense for shielding, robust and reliable operation, and economic viability. Other detector materials and sizes may be used if their suitability has been confirmed.

The detector should be fitted with a collimator (Fig. 1) to define a field of view (FoV) with a diameter of about 15 to 20 cm over the patient's neck covering the entire thyroid, and should be sufficiently shielded against radiation from the remainder of the body, e.g. by a 2 cm thickness of lead (transmission <1 % at 364.5 keV, about 10 % at 637.0 keV and 722.9 keV).

### *Measuring distance*

The individual mean depth of the target tissue activity under the skin is a potential source of error in the determination of absolute uptake values because it influences the measured activity by altering attenuation and the solid angle (inverse-square law). The error increases with decreasing distance. Therefore, the distance between the detector and the patient's neck during the acquisition should be at least 25 cm. Phantom measurements at this distance have shown that the error introduced is about 1.5 % per millimetre deviation of the actual mean depth of the activity from the calibration depth with approximately equal contributions from the changed mass attenuation and the inverse-square law. A corresponding correction might be applied in patients in whom the mean depth of the activity distribution is known to significantly deviate from the calibration depth, e.g. from ultrasound (US) or SPECT imaging. Varying the spacing between neck and probe alters the count rate according to the inverse-square law and must be avoided by ensuring an identical geometry during all measurements. A spacer with negligible attenuation between neck and detector during the count is mandatory to guarantee a reproducible and stable distance. The same spacer in the same position must be used for the calibration measurements with the neck phantom (Fig. 1).

### *Data acquisition*

The detector should be connected to an analyser with energy discrimination, preferably a multichannel analyser to enable spectroscopic measurements with visual control of the energy spectrum. A suitable window depending on the energy resolution of the device should be set symmetrically over the peak at 364.5 keV for the evaluation of the count rate. A fixed multiple of 2–2.5 times the full-width at half-maximum (FWHM) of the peak should be selected as the width of the window leading to inclusion of 98–99.7 % of the counts if the peak profile is gaussian. An energy window of 20 % (width of the window in keV divided by 364.5 keV) is a good choice for most probes. For example, if the width of the peak is 33 keV FWHM, i.e. 9 % energy resolution at 364.5 keV, a window in the range 328–401 keV (20 % or 2.2 times FWHM) is adequate.

Alternatively, the integral counts in the iodine peak at 364.5 keV can be determined by integration of a fitting function.

### *Background correction*

A probe registers not only 364.5 keV radiation originating from the target tissue but also radiation from activity located in other tissues in the FoV and from activity in the remainder of the body outside the FoV penetrating the shielding. Direct penetration of 364.5 keV photons from activity outside the FoV is typically less than 1 % if a well-shielded probe is used, and thus does not require correction. Background from activity within the FoV might be due to $^{131}$I in the blood pool or, in nodular disease, from radioiodine accumulated in unsuppressed healthy thyroid tissue. Only a few percent of the total activity in the blood pool is visible in the FoV and the $^{131}$I concentration in the blood pool declines with time by target tissue uptake, renal clearance, and physical decay. The calculation of the therapeutic activity is mainly

determined by uptake values measured after 24 h or later when the blood pool contribution is typically less than 1 % of the observed count rate. For earlier measurements, a correction might optionally be applied by estimating the blood pool contribution from a measurement in the thigh or the upper arm.

Some background is introduced under the peak at 364.5 keV from 637.0 keV and 722.9 keV radiation scattered in the patient's body or in the detector or shielding and from environmental background. A net count rate corrected for these contributions should be calculated by subtraction of the constant background level measured at the high energy side of the peak at 364.5 keV.

No adequate background correction is possible for residual uptake in healthy thyroid tissue in toxic adenoma with subclinical hyperthyroidism. The target tissue dose is overestimated if the observed count rate is completely attributed to the adenoma [5]. It might be advantageous in these patients to perform the dosimetry with a gamma camera in order to exclusively measure the nodule and to estimate the unintentional dose to the healthy thyroid tissue.

## Gamma camera

### *Gamma camera*

Use of a gamma camera to perform the uptake measurements increases the expense for the dosimetry but can be advantageous in individual patients because it adds information on the distribution of the activity enabling better background correction. A camera with a single head for acquisition of anterior views is sufficient in most cases. It must be suitable for radioiodine scintigraphy with a high-energy collimator with low septal penetration and good imaging characteristics with a full-width at tenth-maximum of the point spread function not exceeding three times the FWHM. If available, a camera with a thick crystal (1/2 inch or 5/8 inch, equivalent to 1.27 cm or 1.59 cm, respectively) should be selected to increase the count rate. Such cameras can be expected to register about 50 counts per second per megabecquerel $^{131}$I (free air) in a 15 % window centred on the peak at 364.5 keV.

### *Measuring distance*

In contrast to probe measurements, no spacer is needed because the dependence of the registered count rate on the distance between detector and activity is not in compliance with the inverse-square law but is determined by the imaging characteristics of the collimator. The distance should be as small as reasonable to improve resolution. Nevertheless, calibration measurements of the sensitivity of detection of activities in a typical target tissue should be made with a phantom (see section Thyroid neck phantom) to allow for attenuation and scatter.

### *Data acquisition*

The count rate in the target tissue is determined from the number of counts at a given acquisition time registered in a region of interest (ROI) drawn on the scintigraphic image over the diseased tissue, e.g. the whole thyroid in Graves' disease or a 'hot' nodule in toxic adenoma. This ROI should include (almost) all counts originating from the target tissue. Another ROI (e.g. over an area caudal and lateral in relation to the target tissue ROI) with count statistics representative of counts registered in the target tissue ROI but not originating in the diseased tissue is assessed for background correction. The count rate in the background ROI is scaled in terms of the ratio of the areas of the target and background regions and is subtracted from the count rate in the target ROI to determine the net target count rate.

## Ultrasound device

The activity required for therapy is linearly dependent on the target mass, and thus a reliable volume measurement is a prerequisite for correct dosimetry. Morphological imaging (for example, computed tomography, magnetic resonance tomography, and two- and three-dimensional US scanning [6–10]), as well as planar and tomographic scintigraphy and positron emission tomography [9, 11–14], have been reported to be suitable for quantifying the mass of the thyroid or of nodules. US is suitable and cost effective and is usually the method of choice for delineating the target volume and for measuring its size. High-resolution US devices equipped with linear or curved array transducers with at least 5 MHz are suitable for imaging and measuring the thyroid lobes or nodules within the thyroid.

The volume can be estimated by approximating the thyroid lobe or the nodule by an ellipsoid. The length $A$ of the volume (long axis of the ellipsoid) and the widths $B$ and $C$ in two orthogonal directions in the central cross-sectional image (short axes) are measured. The mass $M$ in the measured volume can be calculated from the ellipsoid formula and the mass density $\rho$ as $M = \rho \cdot A \cdot B \cdot C \cdot \pi/6$. Studies on the accuracy of this formula are contradictory. Both systematic overestimation [6, 15, 16] and underestimation [8–10, 17] have been reported with corresponding suggestions as to how the algorithm should be modified for the mass estimate. Given the inherent uncertainty introduced by the volume assessment, it is justified in daily routine to calculate $M$ (in grams) simply as $M = A \cdot B \cdot C/2$, with $A$, $B$ and $C$ in centimetres.

The inherent uncertainty introduced by the US volume estimate depends on the shape and size of the target volume and often exceeds 20 %. Larger errors are possible if the

measured volume does not correspond to the metabolically active target tissue. Therefore, the US images should always be compared to the findings of $^{99m}$Tc scintigraphy, which is recommended in the EANM procedure guidelines for therapy of benign thyroid disease [1], in order to verify that the measured volume, e.g. a nodule within the thyroid, corresponds to the accumulating target volume.

### Quality assurance

Quality assurance has to be performed in accordance with local rules and legislation. For detailed information, the reader is referred to the relevant literature, e.g. the EANM guidelines on acceptance testing and quality control of nuclear medicine instrumentation [18, 19]. As a minimum, before starting and during a measurement, the correct measuring geometry must be ensured. The background count rate in the absence of activity sources and the setting of the energy window must be checked each working day. Assessment of the constancy of the sensitivity for a reproducible geometry is recommended at least once a week using an $^{131}$I standard of known activity or a suitable test emitter, e.g. $^{133}$Ba. The simplest and most effective means to ensure a constant sensitivity is to measure the activity to be administered in advance before each administration in both the measuring device and a dose calibrator, and to verify that the measured activity is consistent with that specified by the supplier and that the observed count rate per activity matches the expected sensitivity value of the device.

## Data evaluation

In the following, the formulas for data evaluation are presented without derivation. They are based on theoretical considerations of iodine kinetics and on patient studies [14, 20–30]. The theoretical background and an analysis of the inherent errors of the associated methods for calculating the absorbed dose are provided in the Electronic supplementary material.

### Physical quantities

The following symbols are used for physical quantities:

| | |
|---|---|
| $t$ | Time after administration of the activity |
| RIU($t$) | Fractional $^{131}$I uptake in the target tissue at time $t$ |
| $A_T(t)$ | Activity stored in the target tissue at time $t$ |
| $A_a$ | Administered activity or activity to be administered for therapy |
| $CR_T(t)$ | Net count rate from activity stored in the target tissue at time $t$ |
| $CR_p$ | Net count rate registered for the tracer activity in the phantom |
| $M$ | Mass of the target tissue |
| $D$ | Mean absorbed dose or targeted therapeutic absorbed dose |
| $\bar{E}$ | Mean energy deposited per decay of $^{131}$I in the target tissue |
| $k_t$ | Rate of activity elimination from the blood pool by target tissue uptake |
| $k_p$ | Rate of physical decay, 0.0864 per day for $^{131}$I |
| $k_r$ | Rate of activity elimination from the blood pool by renal clearance |
| $k_h$ | Rate of activity elimination from the target tissue by hormone excretion |
| $k_B$ | $=k_r+k_p+k_t$, rate of activity elimination from the blood pool |
| $k_T$ | $=k_p+k_h$, rate of activity elimination from the target tissue |
| $T_{eff}$ | Effective half-life in the target tissue |
| $T_{est}$ | Estimated effective half-life in the target tissue |
| $t_e$ | Actual time of a measurement 1 or 2 days after activity administration |
| $t_l$ | Actual time of a late measurement 4 to 8 days after activity administration |

A physical unit in square brackets indicates that the specified unit is to be used for the quantity e.g. $M$[g] means the target mass expressed in grams. All times in numerical equations are expressed in days (d) and all transfer rates as per day (d$^{-1}$).

### Radioiodine uptake

The radioiodine uptake RIU($t$) is the fraction of the administered activity $A_a$ that is stored in the target mass at time $t$ after the administration:

$$RIU(t) = \frac{A_T(t)}{A_a} \tag{1}$$

It can be deduced directly from the background-corrected net count rates measured for the tracer activity in the phantom $CR_p$ prior to the administration and for the activity in the target tissue $CR_T(t)$ at time $t$ after the administration:

$$RIU(t) = \frac{CR_T(t)}{CR_p} \tag{1a}$$

RIU($t$) directly reflects the kinetics of radioiodine in the target tissue including physical decay, and no decay correction is applied if $^{131}$I is used for pretherapy dosimetry.

## Calculation of therapeutic activity

The activity necessary to achieve a specified radiation absorbed dose $D$ in the target mass $M$ is:

$$A_a = \frac{1}{\overline{E}} \cdot \frac{M \cdot D}{\int_0^\infty RIU(t)dt} \tag{2}$$

Use of a constant value for the mean energy deposited in the target tissue per decay of $^{131}$I,

$$\overline{E} = 2.808 \frac{Gy \cdot g}{MBq \cdot d} \tag{3}$$

(valid for a thyroid with $M$=20 g) will typically introduce ≤5 % error for masses $M$ ≤90 g and produce results with adequate accuracy for most patients. A simple mass-dependent expression for the factor $1/\bar{E}$ that can be found in Eq. S6 of the Electronic supplementary material may be used for an improved estimate in large goitres.

### *Three or more uptake assessments*

If the dosimetry comprises at least three uptake assessments including measurements at about 4 to 6 h, 1 to 2 days, and 5 to 8 days after activity administration, the uptake function should be approximated by a function describing the iodine transfer into and release from the target mass:

$$RIU(t) = \frac{k_t}{k_B - k_T} \cdot (e^{-k_T \cdot t} - e^{-k_B \cdot t}) \tag{4}$$

Equation 4 can be deduced from a two-compartment model (see the Electronic supplementary material). An example of a fit to measured data is shown in Fig. 2. The therapeutic activity can be calculated from the fit parameters:

$$A_a\,[MBq] = \frac{1}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy] \cdot k_B[d^{-1}] \cdot k_T[d^{-1}]}{k_t[d^{-1}]} \tag{5}$$

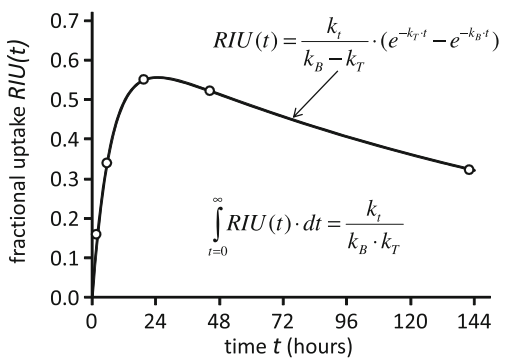


**Fig. 2** Fit of Eq. 4 (*solid line*) to measurements (*circles*) of the fractional target mass uptake RIU(*t*). The residence time (area under the curve) is $k_t \cdot k_B^{-1} \cdot k_T^{-1}$

### *Two uptake assessments*

If two uptake values from measurements at times $t_e$ at 1 or 2 days and $t_l$ at 4 to 8 days after the administration are available with a time interval $t_l - t_e$ of at least 3 days, the effective half-life in the target tissue can be determined by:

$$T_{eff}[d] = \frac{(t_l[d] - t_e[d]) \cdot \ln(2)}{\ln(RIU(t_e)) - \ln(RIU(t_l))} \tag{6}$$

$T_{eff}$ must be set to 8 days (physical half-life of $^{131}$I) if the result calculated from Eq. 6 exceeds this value. The activity to be administered for therapy should be determined from the late uptake assessment at time $t_l$ after the administration:

$$A_a\,[MBq] = \frac{0.714}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy]}{RIU(t_l) \cdot 2^{t_l[d]/T_{eff}[d]} \cdot T_{eff}[d]} \tag{7}$$

Figure 3 shows an example using the last two measurements of the dataset from Fig. 2.

### *One late uptake assessment*

Late uptake measurements have been observed to correlate well with the residence time in the target tissue. The effect is well founded on theory (see the Electronic supplementary material). The therapeutic activity can be estimated from a single uptake assessment 4 to 8 days after the administration according to:

$$A_a\,[MBq] = \frac{0.357}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy]}{RIU(t_l) \cdot t_l[d]} \tag{8}$$

### *One uptake assessment after 1 to 3 days*

If only one early measurement with $t$ between 1 day and less than 4 days is used to determine the therapeutic activity, $A_a$

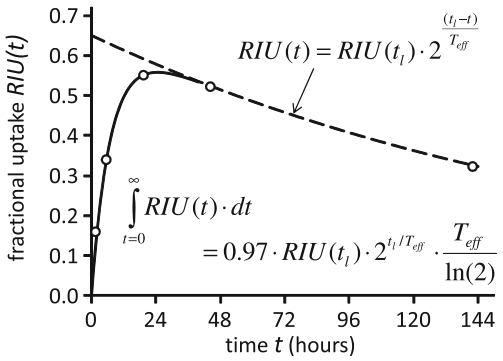


**Fig. 3** Determination of the residence time in the target tissue based on two measurements of the fractional uptake 2 and 6 days after activity administration. The factor 0.97 accounts for the area between the monoexponential decay function (*dashed line*) and the actual uptake function in the phase of accumulation (*solid line*)

should be calculated by:

$$A_a\,[MBq] = \frac{0.714}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy]}{RIU(t_e) \cdot 2^{t_e/T_{est}} \cdot T_{est}[d]}, \qquad (9)$$

with a reasonable estimate $T_{est}$ of the effective half-life. A fixed value, e.g. $T_{est}$=5.5 days, might be used for all patients or disease-specific half-lives if they are known to be representative of the respective patient population.

Accuracy increases with increasing time of the measurement after the administration of $^{131}$I. The potential for error is lower with an early measurement after 48 h than with a measurement after 24 h.

## Standard operational procedures

Pretherapeutic dosimetry is valid only if it is based on a reliable mass estimate and if the kinetics during the therapy are more or less unchanged. Therefore, the target mass should be delineated from current imaging and the following aspects should be considered prior to administration of the activity in order to prevent detrimental effects on the iodine kinetics:

- The time between pretherapeutic dosimetry and therapy should be as short as possible.
- For 2–3 days before and after the activity administrations, medication with antithyroid drugs or thyroid hormones should be identical for pretherapeutic dosimetry and therapy (see Stokkel et al. [1] for recommendations on withdrawal of antithyroid drugs).
- The supply with stable iodine should be identical prior to pretherapeutic dosimetry and therapy, and contamination, e.g. by drugs or nutrition containing considerable amounts of iodine, should be avoided.
- The same method of administration should be used for pretherapeutic dosimetry and therapy; if oral administration is used, intake of food should be suspended from 4 h before to 1 h after the activity administrations to avoid impairment of gastric iodine absorption.
- High fluid intake after administration of radioiodine considerably reduces exposure of the urinary bladder; fluid intake should be at about the same level during pretherapeutic dosimetry and therapy.

### Radiopharmaceutical and tracer preparation

$^{131}$I should be used for pretherapeutic assessment of the biokinetics. The isotopes $^{123}$I and $^{124}$I have been reported to be suitable for iodine kinetics measurements [11, 13, 14], although $^{124}$I is not generally available and its use is limited to specialized centres. $^{123}$I-NaI might be used in exceptional cases to estimate the maximum $^{131}$I-NaI uptake from a measurement 24 h after activity administration. The formulas listed above for the calculation of the therapeutic activity are not applicable to isotopes other than $^{131}$I unless adequate correction for differences in physical decay is applied.

The tracer activity necessary for a reliable assessment of the fractional uptake into the target tissue depends on the equipment used. About 2 MBq of $^{131}$I-NaI is sufficient if the recommended probe with a 5-cm diameter and 5-cm thick sodium iodide crystal is used. This activity leads to about 1,000 counts per percent uptake in the thyroid for a 1-min count. The activity can be reduced if a larger detector or longer acquisition times are used. Up to 10 MBq $^{131}$I might be necessary if a gamma camera is used for the measurements. Higher activities should be avoided because of the potential risk of changing the iodine kinetics in the target tissue by the diagnostic procedure ("stunning"). Lower activities might be necessary to comply with local statutory limits. Administering much lower activities could restrict the available options for calculating the therapeutic activity to the case of one uptake assessment after 1 to 3 days due the increase in statistical errors with later time points particularly in patients showing low uptake and fast iodine turnover.

The tracer activity should be quantified prior to administration in a dose calibrator accurately calibrated for $^{131}$I and quality checked according to acknowledged quality control procedures. If liquid $^{131}$I-NaI is administered, the residual activity must also be quantified to determine the activity administered and to correct correspondingly the count rate measured prior to administration. To ensure radiation safety and to prevent activity sublimation, assessment of activity in the measuring device and subsequent administration should immediately follow the measurement in the dose calibrator.

### Time lines

The schedule of uptake measurements depends on the targeted accuracy and resources available (see section Data evaluation). If a precise determination of the iodine kinetics with information on the thyroidal iodine intake and release is desired at least three measurements are required to estimate the three variables in Eq. 4. The recommended time points are 4 to 6 h, 1 to 2 days, and 5 to 8 days after activity administration. The late time point at 5 to 8 days is needed for reliable determination of the biokinetics, particularly the release of iodinated thyroid hormones that determine the effective half-life in the target tissue. At least two uptake measurements are required if only the residence time in the target volume and the effective half-life are to be determined as part of the pretherapy dosimetry. The accuracy is only slightly reduced with errors typically less than 10 % if the measurements are performed at the recommended time

intervals of 1 to 2 days and 5 to 8 days after activity administration.

In principle, a single measurement after 4 to 8 days is sufficient to estimate the target residence time and thus the activity to be administered for the radioisotope therapy. The accuracy is highest for measurements after 6 days with errors less than 10 % in most patients, and is only slightly reduced for measurements after 5 or 7 days. Data obtained 4 or 8 days after activity administration show systematic errors of >20 % for effective half-lives in the target tissue longer than 6.5 days and shorter than 2.9 days, respectively.

A shortened test with a single measurement 1 to 2 days after activity administration may be used in exceptional cases if measurements of the $^{131}$I uptake at later times are impossible or difficult for organizational reasons. In such cases, the calculation is performed using fixed or disease-related estimates of the effective half-lives. This approach, however, is of very limited accuracy. Errors exceeding a factor of two are possible in individual patients if the uptake is measured after 1 day. The potential for error is slightly lower for uptake assessments after 2 days.

Measuring procedure

The pretherapy dosimetry should include the following tasks:

(a) Target mass delineation by sonography or other suitable procedure.
(b) Quantification of the tracer activity with a dose calibrator.
(c) Measurement of the tracer activity with the test device, probe or gamma camera, with the activity located in the phantom or in free air with the relevant count rate correction.
(d) Verification that the observed count rate per activity matches the expected sensitivity value of the device.
(e) Administration of the tracer activity with accurate documentation.
(f) If liquid $^{131}$I-NaI is administered, measurement of the residual activity and determination of the activity administered and the corresponding count rate.
(g) In-vivo measurements of the $^{131}$I uptake in the target tissue at the times stated in section Time lines.
(h) Calculation of the radioiodine activity needed for therapy according to section Data evaluation.

## Potential sources of error

The evaluation of the therapeutic activity necessary to administer a specified target dose might be erroneous due to:

- Errors in target volume determination
- Inappropriate attenuation correction (no or inadequate phantom)
- Contamination of the phantom
- Incorrect distance between the detector and the patient or phantom
- Deviation of the individual target tissue depth from the calibration depth
- Inappropriate centring of the probe over the phantom or the target tissue (target tissue partially outside the probe's FoV)
- Instability of the electronics of the measuring device, especially if quality control is inadequate
- Variation in background count rate (e.g. from radiation emitted by other patients) for the different uptake measurements
- Reduced or delayed absorption due to recent food intake
- Recent administration of another radionuclide
- Unfavourable choice of timing of the uptake measurements

Furthermore, deviations from the target absorbed dose might occur if the iodine kinetics change between test and therapy due to a change in medication, an iodine-rich diet, radiation damage induced by a high test activity in a small target volume (stunning), or for other unknown reasons, or if the thyroid volume changes during the first days of therapy as reported by Traino et al. [31].



## References

1. Stokkel MP, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. Eur J Nucl Med Mol Imaging. 2010;37:2218–28.
2. European Union. Council Directive 97/43/EURATOM on health protection of individuals against the dangers of ionising radiation in relation to medical exposure. Luxembourg: Council of the European Union; 1997. Available from: http://ec.europa.eu/energy/nuclear/radioprotection/doc/legislation/9743_en.pdf.
3. Salvatori M, Luster M. Radioiodine therapy dosimetry in benign thyroid disease and differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2010;37:821–8.

4. Lassmann M, Chiesa C, Flux G, Bardies M. EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting. Eur J Nucl Med Mol Imaging. 2011;38:192–200.
5. Hammes J, Pietrzyk U, Schmidt M, Schicha H, Eschner W. GATE based Monte Carlo simulation of planar scintigraphy to estimate the nodular dose in radioiodine therapy for autonomous thyroid adenoma. Z Med Phys. 2011;21:290–300.
6. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. Volumetric analysis of thyroid lobes by real-time ultrasound. Dtsch Med Wochenschr. 1981;106:1338–40.
7. Schlögl S, Werner E, Lassmann M, Terekhova J, Muffert S, Seybold S, et al. The use of three-dimensional ultrasound for thyroid volumetry. Thyroid. 2001;11:569–74.
8. Nygaard B, Nygaard T, Court-Payen M, Jensen LI, Soe-Jensen P, Gerhard Nielsen K, et al. Thyroid volume measured by ultrasonography and CT. Acta Radiol. 2002;43:269–74.
9. van Isselt JW, de Klerk JM, van Rijk PP, van Gils AP, Polman LJ, Kamphuis C, et al. Comparison of methods for thyroid volume estimation in patients with Graves' disease. Eur J Nucl Med Mol Imaging. 2003;30:525–31.
10. Reinartz P, Sabri O, Zimny M, Nowak B, Cremerius U, Setani K, et al. Thyroid volume measurement in patients prior to radioiodine therapy: comparison between three-dimensional magnetic resonance imaging and ultrasonography. Thyroid. 2002;12:713–7.
11. Canzi C, Zito F, Voltini F, Reschini E, Gerundini P. Verification of the agreement of two dosimetric methods with radioiodine therapy in hyperthyroid patients. Med Phys. 2006;33:2860–7.
12. Strigari L, Sciuto R, Benassi M, Bergomi S, Nocentini S, Maini CL. A NTCP approach for estimating the outcome in radioiodine treatment of hyperthyroidism. Med Phys. 2008;35:3903–10.
13. Eschmann SM, Reischl G, Bilger K, Kupferschläger J, Thelen MH, Dohmen BM, et al. Evaluation of dosimetry of radioiodine therapy in benign and malignant thyroid disorders by means of iodine-124 and PET. Eur J Nucl Med Mol Imaging. 2002;29:760–7.
14. Matheoud R, Canzi C, Reschini E, Zito F, Voltini F, Gerundini P. Tissue-specific dosimetry for radioiodine therapy of the autonomous thyroid nodule. Med Phys. 2003;30:791–8.
15. Szebeni A, Beleznay E. New simple method for thyroid volume determination by ultrasonography. J Clin Ultrasound. 1992; 20:329–37.
16. Andermann P, Schlögl S, Mader U, Luster M, Lassmann M, Reiners C. Intra- and interobserver variability of thyroid volume measurements in healthy adults by 2D versus 3D ultrasound. Nuklearmedizin. 2007;46:1–7.
17. Knudsen N, Bols B, Bulow I, Jorgensen T, Perrild H, Ovesen L, et al. Validation of ultrasonography of the thyroid gland for epidemiological purposes. Thyroid. 1999;9:1069–74.
18. Busemann Sokole E, Plachcinska A, Britten A. Acceptance testing for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging. 2010;37:672–81.
19. Busemann Sokole E, Plachcinska A, Britten A, Lyra Georgosopoulou M, Tindale W, Klett R. Routine quality control recommendations for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging. 2010;37:662–71.
20. Marinelli LD, Quimby EH, Hine GJ. Dosage determination with radioactive isotopes; practical considerations in therapy and protection. Am J Roentgenol Radium Ther. 1948;59:260–81.
21. Bockisch A, Jamitzky T, Derwanz R, Biersack HJ. Optimized dose planning of radioiodine therapy of benign thyroidal diseases. J Nucl Med. 1993;34:1632–8.
22. Di Martino F, Traino AC, Brill AB, Stabin MG, Lazzer M. A theoretical model for prescription of the patient-specific therapeutic activity for radioiodine therapy of Graves' disease. Phys Med Biol. 2002;47:1493–9.
23. Jonsson H, Mattsson S. Single uptake measurement for absorbed dose planning for radioiodine treatment of hyperthyroidism. Cancer Biother Radiopharm. 2003;18:473–9.
24. Rink T, Bormuth FJ, Braun S, Zimny M, Schroth HJ. Concept and validation of a simple model of the intrathyroidal iodine kinetics. Nuklearmedizin. 2004;43:21–5.
25. Areberg J, Jonsson H, Mattsson S. Population biokinetic modeling of thyroid uptake and retention of radioiodine. Cancer Biother Radiopharm. 2005;20:1–10.
26. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med. 2005;46:1023–7.
27. Carlier T, Salaun PY, Cavarec MB, Valette F, Turzo A, Bardies M, et al. Optimized radioiodine therapy for Graves' disease: two MIRD-based models for the computation of patient-specific therapeutic 131I activity. Nucl Med Commun. 2006;27:559–66.
28. Eckerman K, Endo A. MIRD: Radionuclide data and decay schemes. 2nd ed. New York: Society of Nuclear Medicine; 2008.
29. Merrill S, Horowitz J, Traino AC, Chipkin SR, Hollot CV, Chait Y. Accuracy and optimal timing of activity measurements in estimating the absorbed dose of radioiodine in the treatment of Graves' disease. Phys Med Biol. 2011;56:557–71.
30. Hänscheid H, Lassmann M, Reiners C. Dosimetry prior to I-131-therapy of benign thyroid disease. Z Med Phys. 2011;21:250–7.
31. Traino AC, Di Martino F, Lazzeri M, Stabin MG. Influence of thyroid volume reduction on calculated dose in radioiodine therapy of Graves' hyperthyroidism. Phys Med Biol. 2000;45:121–9.