European Journal of Nuclear Medicine and Molecular Imaging

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

H. Hänscheid[1], C. Canzi[2], W.Eschner[3], G.Flux[4], M. Luster[5], L.Strigari[6], M. Lassmann[1]

[1]Department of Nuclear Medicine, University of Würzburg, Würzburg, Germany; [2]Department of Nuclear Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; [3]Department of Nuclear Medicine, University of Cologne, Cologne, Germany; [4]Joint Department of Physics, Royal Marsden NHS Foundation Trust & Institute of Cancer Research, Sutton, UK; [5]Department of Nuclear Medicine, University of Ulm, Ulm, Germany; [6]Laboratory of Medical Physics and Expert Systems, National Cancer Institute Regina Elena, Rome, Italy.

Physical background and rationale

^{131}I, Radioiodine

The neutron rich iodine isotope ^{131}I, radioiodine, is used for the treatment of thyroid disorders. It decays to the stable isotope ^{131}Xe by emission of beta and gamma rays. Fig. S1 shows the main transitions with intensities of more than 1% per decay [1].

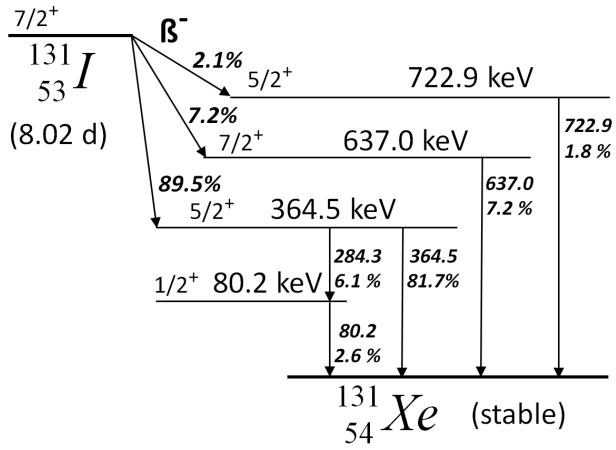

Fig. S1 *Radioiodine decay scheme*

The energy release per decay is 971 keV with mean contributions of beta and gamma radiation of 192 and 383 keV, respectively. While the primary gamma emission (364.5 keV, 81.7%) is usable for scintigraphic imaging, the therapeutic effect is almost completely due to local energy deposition by beta radiation. The average range of the beta particles in soft tissue is approximately 0.4 mm. At about the same distance from accumulating target tissue, the absorbed dose from beta radiation drops to less than 10% of that within the target volume.

Radiation absorbed dose

The radiation absorbed dose is defined as the energy E deposited by ionizing radiation in a target mass M, which might be the whole thyroid or a hyper-functioning part of the thyroid. It is measured as joules per kilogram and represented by the equivalent SI unit, gray [Gy]:

$$D[Gy] = \frac{E[J]}{M[kg]} \qquad \text{(S1).}$$

Neglecting energy deposition from decays outside the target, E is the mean energy $\bar{E}$ deposited per decay of ^{131}I in the target volume multiplied by the number of decays, which in turn is represented by the time integral over the activity $A_T(t)$ in M:

$$D = \frac{\overline{E} \cdot \int_0^\infty A_T(t)dt}{M} = \frac{\overline{E} \cdot A_a \cdot \int_0^\infty RIU(t)dt}{M} \qquad \text{(S2).}$$

In Eq. S2, 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:

$$RIU(t) = \frac{A_T(t)}{A_a} \qquad \text{(S3).}$$

The time integral over $A_T(t)$ is being referred to as "time-integrated activity" in recent MIRD terminology or formerly "cumulated activity" [2]. It is equivalent to the administered activity A_a multiplied by the time integral over the fractional uptake $RIU(t)$ in the target volume, termed "time-integrated activity coefficient" or formerly "residence time" RT [2].

From Eq. S2, the activity necessary to achieve a specified radiation absorbed dose D in the target mass M is calculated to be:

$$A_a = \frac{1}{\overline{E}} \cdot \frac{M \cdot D}{\int_0^\infty RIU(t)dt} = \frac{M \cdot D}{\overline{E} \cdot RT} \qquad \text{(S4).}$$

Mean energy $\bar{E}$ deposited per decay of ^{131}I

The mean energy $\bar{E}$ being deposited in the target tissue per decay of ^{131}I depends on the size and the shape of mass *M*. $\bar{E}$ increases with *M* because the fraction of energy lost by beta radiation that is produced at the edge of the target volume and leaves that volume decreases and more energy is imparted by gamma radiation. The mean energy release per decay [Bq·s] by beta radiation is 192 keV/Bq/s or, converted to more convenient units, 2.654 Gy·g/MBq/d [1]. The fractional energy deposition due to interaction of gamma rays is approximately 5% in a thyroid with 20 g mass (approximated by two spheres with 10 g each [3]):

$$\overline{E} = 2.808 \frac{Gy \cdot g}{MBq \cdot d} \qquad \text{(S5)}$$

and about 10% in an organ with 90 g mass.

Thus, use of Eq. S5 for the calculation of the activity to be administered will produce results with adequate accuracy in most of the cases.

A simple mass dependency can be introduced if the mass *M* is approximated by two spheres of mass *M*/2 each. Figure S2 shows the expected values for the factor $1/\bar{E}$ for different masses *M* as taken from calculations with the sphere model in OLINDA [3].

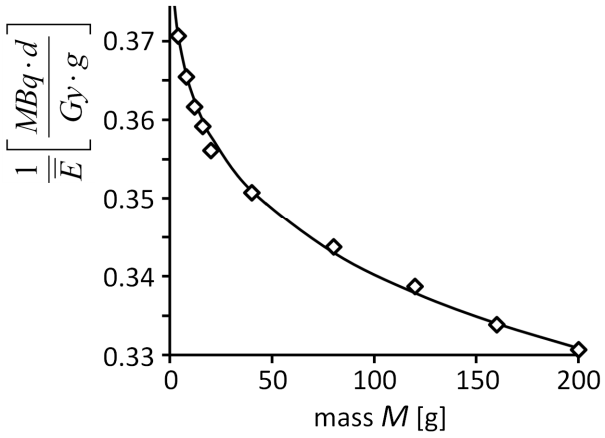

Fig. S2 *Expected values for the factor $1/\bar{E}$ for different masses M and empirical fit.*

The empirical fit to the data in Fig. S2 is given by:

$$\frac{1}{\overline{E}} = \frac{7.2}{(M[g])^{0.25} + 18} \frac{MBq \cdot d}{Gy \cdot g} \qquad \text{(S6).}$$

The fit can be used as mass dependent estimate for the factor $1/\bar{E}$ in Eq. S4.

Determination of the therapeutic activity

An estimate for the time integral in the denominator of Eq. S4 can be obtained by a compartment model fit to measurements of *RIU(t)*. Rather detailed and complex models for the intra- and extra-thyroidal iodine kinetics can be found in the literature. They might be adequate for the study of biokinetics and metabolism but require an expenditure regarding the number and the accuracy of measurements which is not justified in daily routine. Simple models suffice to estimate the residence time in the target tissue.

Two compartment model

Given the uncertainties introduced by the target mass estimate, the quantification of *RIU(t)*, and the specification of the required dose, a model with 2 compartments (Fig. S3) is adequate to deduce the function to be fitted to the retention measurements.

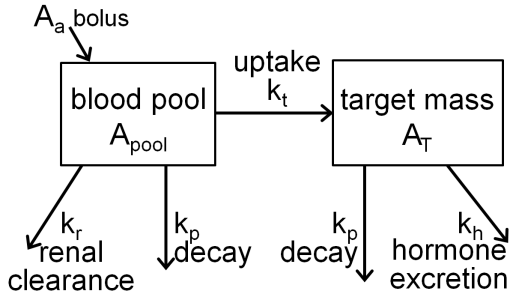

Fig. S3 *Model of the ^{131}I kinetics in benign thyroid disease with 2 compartments, blood pool and target mass. A_x denote activities, k_x transfer rates.*

The activities in blood A_{pool} and target mass A_T are:

$$A_{pool}(t) = A_a \cdot e^{-(k_r + k_p + k_t) \cdot t} \qquad \text{(S7),}$$

$$\frac{dA_T(t)}{dt} = k_t \cdot A_{pool}(t) - (k_p + k_h) \cdot A_T(t) \qquad \text{(S8),}$$

with the transfer rates for target uptake k_t, physical decay k_p (0.0864/d for ^{131}I), renal clearance k_r, and hormone excretion from the thyroid k_h.

Solving the differential Eq. S8 yields:

$$\begin{aligned} \frac{A_T(t)}{A_a} &= RIU(t) \\ &= \frac{k_t}{k_r + k_t - k_h} \cdot (e^{-(k_p + k_h) \cdot t} - e^{-(k_r + k_p + k_t) \cdot t}) \\ &= \frac{k_t}{k_B - k_T} \cdot (e^{-k_T \cdot t} - e^{-k_B \cdot t}) \end{aligned} \qquad \text{(S9),}$$

with $k_B=k_r+k_p+k_t$ and $k_T=k_p+k_h$ being the rates of activity elimination from the blood pool and the target tissue, respectively. The maximum uptake is reached after

$$t_{\max} = \frac{\ln(k_B) - \ln(k_T)}{k_B - k_T} \qquad \text{(S10);}$$

which can be calculated by inserting t_{max} into Eq. S9.

The residence time is calculated by integration of *RIU(t)* over time to be:

$$RT = \frac{k_t}{k_B - k_T} \cdot \left(\frac{1}{k_T} - \frac{1}{k_B}\right) = \frac{k_t}{k_B \cdot k_T} \qquad \text{(S11).}$$

At least 3 measurements of the target tissue uptake are required for an estimate of the 3 unknown transfer rates in Eq. S9. Some error in the individual values of the transfer rates is introduced mainly due to neglect of

- the gastro-intestinal-tract compartment after oral intake,
- the initial increase of the compartment blood pool due to diffusion into cellular tissues and extra-cellular fluid spaces, and of
- deiodination after hormonal release followed by thyroidal re-absorption.

The residence time estimate in Eq. S11, however, is expected to approximate the actual value with reasonable accuracy. Recommended time points for the measurements are 4 to 6 hours, 1 to 2 days, and 5 to 8 days after the activity administration.

Figure S4 shows an example of a fit of Eq. S9 to a set of 5 measurements of *RIU(t)*.

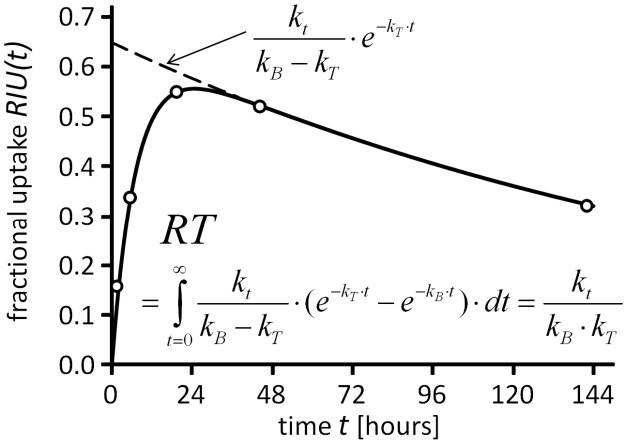

Fig.S4 *Fit of Eq.S9 (solid line) to measurements (circles) of the fractional target mass uptake RIU(t). The dashed line is a mono-exponential decay approaching the solid line after the phase of accumulation.*

After fit and determination of the transfer rates, the therapeutic activity can be calculated from Eq. S4 and Eq. S11 to be:

$$A_a\,[MBq] = \frac{1}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy] \cdot k_B[d^{-1}] \cdot k_T[d^{-1}]}{k_t[d^{-1}]} \qquad \text{(S12).}$$

One compartment model

An approach often used to calculate A_a from uptake measurements over several days is to consider a model with only one compartment, the target tissue. In this model the activity in the target decays mono-exponentially with an effective half-life T_{eff} that is calculated from measured data with $t \geq 24$ h. The method requires at least two uptake measurements at 1 or 2 days (t_e) and after 4 to 8 days (t_l) after the activity administration and reasonable assumptions on the uptake function up to t_e which adequately take the phase of accumulation namely the reduction by the second addend in Eq. S11 (area between dashed and solid lines in Fig. S4) into account.

It can be calculated from Eq. S11 that the second addend reduces the residence time by about 3% in a typical patient with benign thyroid disease ($k_r = 2.08$/d or 8 h half-life of renal clearance, $k_h = 0.05$/d or 5 d effective half-life of thyroidal activity, $k_t = 2.08$/d or about 50% maximum uptake). The fraction will be higher in patients with low uptake and slow renal clearance. It has been observed in a retrospective analysis in a typical population that the reduction of residence time due to the second addend in Eq. S11 is 3 ± 3% in 96% of the patients. The maximum observed value was 8.3% [4]. The phase of accumulation can therefore be accounted for by neglecting the second addend in Eq. S11 and introducing a factor of 0.97 to the residence time.

If mono-exponential decay is assumed between t_e and t_l, T_{eff} is:

$$RIU(t_l) = RIU(t_e) \cdot e^{-(t_l - t_e) \cdot \ln(2)/T_{eff}}$$

$$\Rightarrow T_{eff}[d] = \frac{(t_l[d] - t_e[d]) \cdot \ln(2)}{\ln(RIU(t_e)) - \ln(RIU(t_l))} \qquad \text{(S13).}$$

From the extrapolation of the uptake function from the late measurement at time t_l to time zero $RIU(t_l) \cdot 2^{t_l/T_{eff}}$ and with the reduction factor 0.97 accounting for the phase of accumulation, the residence time becomes

$$RT = 0.97 \cdot RIU(t_l) \cdot 2^{t_l/T_{eff}} \cdot \frac{T_{eff}}{\ln(2)} \qquad \text{(S14)}.$$

If two uptake measurements are used to determine the therapeutic activity, the measurements should be at times t_e at 1 or 2 days and t_l after 4 to 8 days after the administration of the tracer activity with a time interval t_l-t_e of at least 3 days. A_a should be calculated according to Eq. S15 (deduced from Eq. S4 and Eq. S14):

$$A_a[MBq] = \frac{0.714}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy]}{RIU(t_l) \cdot 2^{t_l/T_{eff}} \cdot T_{eff}[d]} \qquad \text{(S15)}.$$

One late measurement

The factor $2^{t_l/T_{eff}} \cdot T_{eff}$ in the denominator of Eq. S15 is almost independent of T_{eff} deviating less than 6% from the factor $2 \cdot t_l$ if $0.45 \cdot t_l < T_{eff} < 1.17 \cdot t_l$ [4] (Fig. S5).

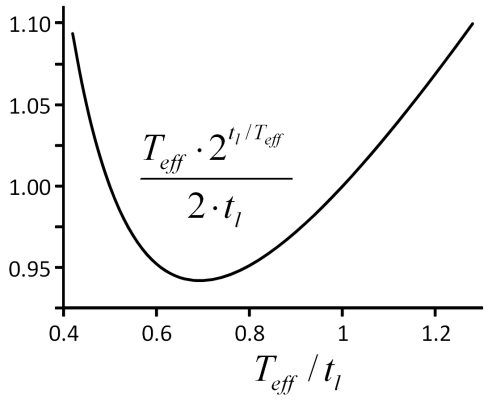

Fig. S5 *The factor* $2^{t_l/T_{eff}} \cdot T_{eff}/(2 \cdot t_l)$ *deviates less than 6% from unity if* $0.45 < T_{eff}/t_l < 1.17$

Thus, an estimate for the therapeutic activity, which is independent of the actual effective half-life of the activity in *M*, can be obtained from a single late measurement at time t_l by:

$$A_a[MBq] = \frac{0.357}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy]}{RIU(t_l) \cdot t_l[d]} \qquad \text{(S16)}.$$

The error potential is lowest for measurements after $t_l = 6$ d with deviations less than 10% if T_{eff} is between 2.5 d and 7.8 d, which applies to most of the patients. While accuracy is only slightly reduced for measurements after 5 or 7 days, data obtained after 4 or 8 days introduce systematic errors >20% for $T_{eff} > 6.5$ d and $T_{eff} < 2.9$ d, respectively.

One early measurement

Equation S16 is not applicable for early measurements at times $t_e < 4$ d. If only one early measurement is used to determine the therapeutic activity, A_a is calculated by

$$A_a[MBq] = \frac{0.714}{\overline{E}} \cdot \frac{M[g] \cdot D[Gy]}{RIU(t_e) \cdot 2^{t_e/T_{est}} \cdot T_{est}[d]} \qquad \text{(S17)}.$$

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

This method is clearly inferior due to the large inter-individual variation in T_{eff} even for the same disease. Large errors up to a factor of two are possible if the actual half-life T_{eff} differs considerably from the presumed value T_{est} [4]. The accuracy increases with increasing time of measurement after the administration of ^{131}I [4]. An early measurement after 48 h reduces the error potential as compared to 24 h.

References

[1] Eckerman KF, Endo A. MIRD: Radionuclide Data and Decay Schemes, 2nd edition. Reston; 2008

[2] Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD Pamphlet No.21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature. J Nucl Med 2009; 50:477–484

[3] 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

[4] Hänscheid H, Lassmann M, Reiners C. Dosimetry prior to I-131 Therapy of Benign Thyroid Disease. Z Med Phys. 2011;21::250-7.

Example

The following worked example of a pre-therapeutic dosimetry with a complete set of data including 5 assessments of the target tissue uptake shows the measuring tasks according to 'Standard operational procedures – Measuring procedure' of the SOP and the determination of the therapeutic activity.

Patient and equipment

A 70 years old patient with toxic multi-nodular goitre is scheduled for radioiodine therapy with a prescribed radiation dose to the thyroid of D = 150 Gy.

Pre-therapeutic dosimetry is performed with a dedicated collimated probe with a typical sensitivity for an ^{131}I activity in a neck phantom of 22,350 counts per min (cpm) per MBq in a 20% window (328 - 401 keV) around the peak at 364.5 keV.

Measuring procedure

a. Target mass delineation by sonography or other suitable procedure.

The dimensions A · B · C (see SOP 'Ultrasound device') of the left and right thyroid lobes are measured by ultrasound to be 3.2 cm · 3.8 cm · 6.2 cm and 2.7 cm · 2.8 cm · 5.9 cm, respectively. The correspondent masses according to the formula $M[g] = A[cm] \cdot B[cm] \cdot C[cm] / 2$ are 37.7 g and 22.3 g which adds up to a target mass of M = 60 g.

b. Quantification of the tracer activity with a dose calibrator.

A capsule with ^{131}I is used for dosimetry. The activity is measured with a dose calibrator immediately prior to the probe measurement to be 1.22 MBq.

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.

Prior to the capsule measurement, the background count rate is measured for quality assurance with the neck phantom in the absence of any activity source and checked to match the typically observed value. This excludes any contamination during the subsequent count of the capsule in the phantom. The observed background count rate is documented.

The measurement with the capsule in the phantom yields a count rate in the window around the peak at 364.5 keV (width: 73 keV) of 27,133 cpm. Visual inspection verifies that the line is well within the window. The count rate of 127 cpm in a 40 keV background window at the high energy side of the peak (410 - 450 keV) is used to correct for the constant background under the peak (see SOP 'Probe – Background correction'). The net count rate is calculated to be

$$27{,}133\ cpm - \frac{127\ cpm}{40\ keV} \cdot 73\ keV = 26{,}901\ cpm \cdot$$

d. Verification that the observed count rate per activity matches the expected sensitivity value of the device.

The net count rate per activity 26,901 cpm / 1.22 MBq = 22,050 cpm/MBq is in good agreement (98.7%) with the expected value of 22,350 cpm/MBq. The calculation proves the proper functioning of the device and is documented as a quality control.

e. Administration of the tracer activity with accurate documentation.

The capsule is administered to the patient immediately after the probe measurement. The activity and count rates as well as the time of administration (12-Jan-11 09:26) are documented.

f. If liquid ^{131}I-NaI is administered, measurement of the residual activity and determination of the activity administered and the corresponding count rate.

Not applicable.

g. In-vivo measurements of the ^{131}I uptake in the target tissue at the times stated in section SOP 'Time lines'.

The count rates listed in the following table are observed in in-vivo assessments over the patient's neck at the same distance as the measurement with the capsule in the phantom. *Peak* and *BKG* denote the peak and background count rates in cpm in the windows 328 - 401 keV (width: 73 keV) and 410 - 450 keV (width: 40 keV), respectively. *Net* is the peak count rate corrected for the constant background (SOP 'Probe – Background correction') calculated as $Net = Peak - BKG \cdot 73 / 40$. The target uptake *RIU(t)* is calculated with Eq. 1a (SOP 'Data evaluation – Radioiodine uptake')

		Assessment no.				
		#1	#2	#3	#4	#5
Date		12-Jan-11	12-Jan-11	13-Jan-11	14-Jan-11	18-Jan-11
Time		11:32	15:12	08:04	08:23	08:11
t	/days post administration	0.09	0.24	0.94	1.96	5.95
Peak	/cpm	3,689	8,028	13,630	13,277	9,017
BKG	/cpm	198	143	124	118	104
Net	/cpm	3,328	7,767	13,404	13,062	8,827
RIU(t)		0.124	0.289	0.498	0.486	0.328

h. Calculation of the radioiodine activity needed for therapy according to section SOP 'Data evaluation'.
Data from 5 uptake assessments including measurements at about 4 to 6 hours, 1 to 2 days, and 5 to 8 days after the activity administration are available. The therapeutic activity A_a is calculated according to SOP 'Data evaluation - Three or more uptake assessments'. A fit of the uptake data to SOP Eq. 4 yields the transfer rates k_t = 1.669 / d, k_T = 0.0974 / d, and k_B = 2.941 / d. A_a is calculated from SOP Eq. 5 to be A_a = 550 MBq.

Optional calculations

In this section, the therapeutic activity and other parameters are calculated from subsets of uptake data to illustrate the computational procedures. The following table lists the determined parameters together with the equations in the SOP (in brackets) used to deduce the values.

Parameter / unit			Subset of assessments							
			all	#2,#3,#5	#2,#4,#5	#2,#5	#3,#5	#5	#3	#4
k_t	/ d^{-1}	(Fit to	1.669	1.710	1.697					
k_T	/ d^{-1}	Eq.4)	0.0974	0.0965	0.0996					
k_B	/ d^{-1}		2.941	3.034	3.022					
t_{max}	/ d	(Eq.S10)	1.20	1.17	1.17					
$RIU(t_{max})$		(Eq.4)	0.505	0.503	0.500					
T_{eff}	/ d		7.1	7.2	7.0	8.3	7.1			
				(= ln(2)/k_T)		(Eq.6)				
A_a	/ MBq		550	549	568	521[1)]	551	586	742	670
				(Eq.5)		(Eq.7)		(Eq.8)	(Eq.9)[2)]	
Deviation[3)] / %			0	-0.3	+3.3	-5.4	+0.1	+6.5	+35	+22

1) T_{eff} was set to 8 d to calculate A_a
2) T_{est} = 5.5 d was used to calculate A_a
3) % deviation from the value determined from the complete set of data $\left(= \frac{A_a}{550\,MBq} - 100\%\right)$