Dosimetry for Nuclear Medicine Imaging and Therapy Guidance from MIRD and ICRU

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Harmonization of the MIRD and ICRP Schema for Internal Dosimetry

The radiation absorbed dose to internal organs of a patient following the administration of a radiopharmaceutical for either diagnostic or therapeutic purposes is not a directly measurable quantity, and thus it must be computed using an internal dosimetry formalism based upon typically a combination of pre-computed quantities and data obtained by measurement on the individual patient.

The original mathematical methods, models, equations, nuclear decay data, and biokinetic parameters needed for computing radiation absorbed dose to internal organs were developed by the Medical Internal Radiation Dose (or MIRD) Committee of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) in the early 1960s. The most recent revision of the MIRD schema for internal organ dosimetry was published in 2009 as MIRD Pamphlet No. 21 in the Journal of Nuclear Medicine. In mid-2021, the MIRD Committee will release *MIRD Primer 2020 – A Complete Guide To Radiopharmaceutical Dosimetry*.

In the 1970s, the International Commission on Radiological Protection (ICRP) developed its own set of expression, quantities, and terminology for the same purpose – estimating dose to internal organs following intake of both radionuclides and radiopharmaceuticals. With the issue of ICRP Publication 130 (in 2015) and ICRP Publication 133 (in 2016), however, a harmonization of the dosimetry schema for internal organ dosimetry was made, thus providing a consistent terminology and approach to the field of internal dosimetry.





MIRD PRIMER 2020

A Complete Guide to Radiopharmaceutical Dosimetry

Prepared by the MIRD Committee of the Society of Nuclear Medicine and Molecular Imaging: Rachel M. Bartlett, Wesley E. Bolch, A. Bertrand Brill, Yuni K. Dewaraja, Frederic H. Fahey, Darrell R. Fisher, Robert F. Hobbs, Roger W. Howell, Ruby F. Meredith, Joseph G. Rajendran^{*} George Sgouros (Immediate Past Chairman), Pat Zanzonico (Chairman)



MIRD Schema - Mean Absorbed Dose Rate

The mean absorbed dose $D(r_T)$ is defined as the mean energy imparted to target tissue (or region) r_T per unit tissue mass. The rate at which the absorbed dose is delivered $\dot{D}(r_T, t)$ to target tissue r_T within a patient from a radiopharmaceutical distributed uniformly within source tissue r_S at time *t* following radiopharmaceutical administration is given as:

$$\dot{D}(r_T,t) = \sum_{r_S} A(r_S,t) \ S(r_T \leftarrow r_S,t)$$

where

 $A(r_S, t)$ is the time-dependent activity of the radiopharmaceutical in source tissue r_S and

 $S(r_T \leftarrow r_S, t)$ is a quantity called the radionuclide S value.

We first note that this expression involves a summation over all possible source regions r_s that might contribute absorbed dose to the target region r_T . For short-range radiations emitted by the radionuclide, the relevant source tissue may only be the target tissue itself (i.e., $r_T = r_s$).

For source tissues which emit photons (gamma-rays or x-rays), the relevant source tissues may be adjacent to or even at a distance from the target tissue (i.e. $r_T \neq r_S$) and may also include the target tissue itself (i.e., $r_T = r_S$).

The time-dependent activity $A(r_s, t)$ represents the rate of nuclear decays in the source tissue r_s at time t, while the S value represents the absorbed dose rate to the target tissue r_T per radionuclide unit activity in the source region tissue r_s also at time t.





MIRD Schema - Mean Absorbed Dose

In the previous equation, the absorbed dose rate to the target tissue r_T is shown to be given as the sum of the product of two terms – the activity of the radiopharmaceutical activity in the source tissue $A(r_S, t)$ and the radionuclide S value for the source/target organ pair of interest $S(r_T \leftarrow r_S, t)$.

While the first term is clearly a function of time since administration, the second term – the S value – may typically be considered not to vary with time during the period when the absorbed dose is delivered. Thus, the corresponding expression for the mean absorbed dose $D(r_T, \tau)$ to target tissue r_T may be written as:

where $\tilde{A}(r_s, \tau)$ is the *time-integrated activity* (TIA) in source tissue r_s over dose-integration period. The time-integrated activity represents the total number of decays with the source organ.



Simplified kinetics model of the accumulation and elimination of radioactivity in a source organ (e.g., liver). A fraction (f) of the injected activity (A_0) is localized in the source organ in which the initial activity (A_f) is reduced by physical decay and biologic excretion of the radiopharmaceutical.

MIRD Schema – Curve Fitting and Time Integration



Time-integrated activity (TIA)

$$\widetilde{A}(r_S,\tau) = \int_0^\tau A(r_S,t) dt$$

Time-integrated activity coefficient (TIAC)

$$\widetilde{a}(r_S,\tau) = \int_0^\tau \frac{A(r_S,t)}{A_0} dt$$

Figure 5.9. Data points showing an uptake followed by exponential clearance. Functions fit to the data were (a) a single exponential, and (b) a sum of two exponentials with four parameters (a, b, c, and d) of the form $y = a \exp(-bt) + c \exp(-dt)$.





 Table 5.1.
 Summary of common mathematical forms that may be considered and tested for describing the uptake and clearance kinetics of radiopharmaceuticals.

	Function	Functional form
1	Single exponential	$a \exp(-bt)$
2	Sum of two exponentials, 4 terms	$a \exp(-bt) + c \exp(-dt)$
3	Sum of three exponentials, 6 terms	$a \exp(-bt) + c \exp(-dt) + e \exp(-ft)$
4	Rational function	$(a+bx)/(1+cx+dx^2)$
5	Uptake-clearance, 3-term product	$[1 - \exp(-at)] b \exp(-ct)$
6	Uptake-clearance, 4-term product	$[1 - a \exp(-bt)] c \exp(-dt)$
7	Difference of two exponentials, 3 terms	$a[\exp(-bt) - \exp(-ct)]$
8	Difference of two exponentials, 2 terms	$\exp(-at) - \exp(-bt)$
9	Hoerl function	ab^tt^c a
10	Trapezoidal integration	y = ax + b, over each interval between consecutive data points: linear spline (piecewise straight-line function)



Radionuclide S-Value

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The S value is characteristic of the radionuclide and the anatomic model chosen to represent the internal body anatomy of the patient.

In many cases, "reference" anatomic models are used to compute the S value. These may be anatomic models of either the avera ged sized male or female patients at fixed ages – newborn, 1-year-old, 5-year-old, 10-year-old, 15-year-old, and the adult. This choice of a "reference" patient is perfectly adequate for patient organ dosimetry under the MIRD schema for diagnostic nuclear medicine.

In radionuclide therapy, however, it may be desirable to compute S values that are truly unique to the individual organ anatomy of the patient based upon CT or MR images.



Frontal views of the ICRP reference voxel phantom series as given in ICRP Publication 110 (adults) and ICRP Publication 143 (pediatric series).

$$S(r_T \leftarrow r_S) = \frac{1}{M(r_T)} \sum_i E_i Y_i \phi(r_T \leftarrow r_S, E_i)$$
$$= \sum_i \Delta_i \Phi(r_T \leftarrow r_S, E_i)$$

 $\phi(r_T \leftarrow r_S, E_i)$ = Absorbed Fraction (AF) $\Phi(r_T \leftarrow r_S, E_i)$ = Specific Absorbed Fraction (SAF)

Radionuclide S-Value

Technical Note: Patient-morphed mesh-type phantoms to support personalized nuclear medicine dosimetry — a proof of concept study

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FIG. 1. Phantoms derived from PET/CT segmentation, and morphing of reference phantom via deformable image registration. (a) Volume-rendered CT and exterior surfaces of segmented phantom (red), rigidly co-registered reference phantom (blue), and deformably co-registered reference phantom (green). Note the improved match of exterior body contour evident by visual assessment, of the deformed phantom relative to the original (rigidly co-registered) phantom. (b) Volume-rendered CT windowed for bone contrast; interior organs of each phantom. (c) Phantom surface cross-section superimposed on coronal (left), sagittal (middle) and axial (right) CT slices. Arrows represent deformation vectors applied to reference phantom.

Multi-Scale Implementation of the MIRD Schema



FI

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D

А

В



C





Image Voxels

Cells and **Cell Clusters**

Macro-to-Micro Extension of the MIRD Schema for Alpha Radiopharmaceutical Therapy

A nephron-based model of the kidneys for macro-to-micro α -particle dosimetry

Phys. Med. Biol. 57 (2012) 4403-4424

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$$D(TC) = \sum_{SC} g(SC) \widetilde{A}(organ) S(TC \leftarrow SC)$$

SC – source compartment (e.g., proximal tubules) **TC** – target compartment (e.g., glomerulus)

 $\widetilde{A}(organ)$ - time-integrated activity imaged in the RPT patient

 $S(TC \leftarrow SC)$ – microscale radionuclide S values for source/target compartments g(SC) – time integrated activity apportionment factor

Microscale S values – derived from either stylized models of organ microstructure, or developed through 3D tissue histology reconstructions. **TIA apportionment factors** must be developed through preclinical animal models to be extrapolated to the human patient.



Table 2. Human microscale S values for the ²²⁵Ac decay chain for both the unit and compartmental nephron model.

	S-value (u)	Absorbed energy		S-value (c)
²²⁵ Ac	(Gy/Bq-s)	(MeV/decay)	%	(Gy/Bq-s)
glc←glc	5.70E-05	5.24	88.07	1.85E-10
glc←prt	5.39E-06	0.75	12.61	6.08E-13
$prtc \leftarrow glc$	3.02E-05	0.096	1.61	3.12E-12
prtc ← prtc	4.54E-05	1.28	21.51	4.69E-12
prtc ← prtl	4.49E-05	1.76	29.58	4.64E-12
prtc ← prts	4.52E-05	1.53	25.71	4.66E-12
kid←kid	_	5.95	100.00	3.17E-12
cor←cor	_	5.95	100.00	4.82E-12



Introduction to MIRDsoft.org

- <u>The MIRDsoft.org effort is requesting</u> <u>formal endorsement from SNMMI board -</u> <u>and permission to use SNMMI MIRD logo</u>
- The SNMMI MIRD committee has embarked on effort to make a suit of free dosimetry-supporting software tools
 - Software distribution
 - Online community
 - Scalable innovation
- Status: website ready to go live with MIRDcalc and MIRDcell v2

Supported with oversight and funding



MIRDcalc is a NIH/NIBIB U01

(Bolch/Kesner) grant supported project to make free dosimetry tools for the community

- UF and MSK collaboration
- Funded for 5 years
- NM dosimetry, CT dosimetry, Curvfitting, Monte Carlo
- All free for community



MIRDcell is a **R01** (Howell) grant supported project to build free cellular level dosimetry tool for the community

MIRD

Funded for 5 years

<u>calc</u>

• Free for community



MIRDsoft.org

Radiation Dosimetry Community Platform

MIRD

MIRDcell Version 3 Howell, Roger W. Rutgers University, Newark, NJ, Uni

MIRD

cel





ICRU Reports in the Field of Radiotherapy



September 1993

UNIVERSITY of

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ORIDA



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Complete clinical work-up (site and extent of tumor, stage,

morphologic type etc.)

Decision on external beam

therapy and prescription of treatment

Localization-simulation

Acquisition of additional anatomical

data for dose planning

Delineation of volumes

Provisional selection of beam arrangements and computation of

corresponding dose distribution

Steps in the radiotherapy procedure. There should be a continuous feed-back between all the different steps. A difficulty at a given point may question all the decisions made at previous steps



Gross Tumor Volume (GTV) denotes the demonstrated tumor.

Clinical Target Volume (CTV) denotes the demonstrated tumor (when present) and also volumes with suspected (subclinical) tumor.

Planning Target Volume (PTV) consists of the CTV(s) and a margin to account for variations in size, shape, and position relative to the treatment beam(s).

Treated Volume is the volume that receives a dose that is considered important for local cure or palliation.

Irradiated Volume is the volume that receives a dose that is considered important for normal tissue tolerance (other than those specifically defined for organs at risk).



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Brachytherapy - 2016

Small Photon Fields - 2017

Light Ion Beams - 2019

DOSIMETRY-GUIDED RADIOPHARMACEUTICAL THERAPY

25
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345
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Appendix A – Clinical Examples

A.1¹³¹ Nal Treatment of Benign Thyroid Disease

A.2 Treatment of Neuroendocrine Tumors using ¹⁷⁷Lu-DOTATATE

A.3 ⁹⁰Y Radioembolization

A.4 Treatment of Hormone Sensitive Prostate Cancer using ¹⁷⁷Lu-PSMA



Chapter 5 – Conceptual Framework for RPT Patient Dosimetry

General Principles

- Unlike systemic cancer therapies in general, the use of radioactively labelled pharmaceuticals results not only in molecularly targeted, internal radiotherapy, but also offers the possibility of imaging or measuring the pharmacokinetics of the radiopharmaceutical in the patient during the therapy.
- In many cases prospective or pre-therapeutic imaging or measurement is possible by use of a pre-therapeutic dosage of the same pharmaceutical or a surrogate, such as a theranostic companion drug (e.g. ¹¹¹In- and ⁹⁰Yibritumomab tiuxetan).
- Pre-therapy and within-therapy imaging or measurements opens the possibilities of patient-specific absorbed dose planning and verification, which is common practice for other radiotherapy modalities.



Previous External Beam ICRU Reports

Patient Representation

The patient representation obtained from medical imaging is the volume over which dose from external beams may be computed. Ideally it represents the entire patient anatomy.

Terminology for Irradiated Tissues

Irradiated Volume

Volume over which the primary external beam passes including the patient, patient support and patient immobilization systems. All of the irradiated volume of the patient must be in the patient representation with generous superior and inferior borders. The patient representation must contain all of the patient's irradiated volume.



This ICRU Report on RPT

Localization Region

The organs, tissues, or cells to which the radioactive compound localizes.

Terminology for Irradiated Tissues

Source Region (SR)

The organs and tissues for which the activity content as a function of time and the time-integrated activity are estimated. The Source Region (SR) is a subcategory of the Localization Region. The SR is categorized into the Delineable Source Region(s) (SR_D) and the Non-Delineable Source Region(s) (SR_{ND}), depending on the possibility to perform patient-specific image-based estimates of the timeintegrated activity, and the level of uncertainty in the absorbed dose estimate.

Terminology for Irradiated Tissues

Gross Tumor Volume (GTV) and Clinical Target Volume (CTV)

Region(s) of disease for which the mass and absorbed dose are estimated. The GTV and CTV are subregions of the PTV. The GTV is delineated with clinical and imaging evidence. The CTV is an extension of the GTV (such that the GTV is a subregion of the CTV) delineated to include suspected microscopic extension or may be regions for which disease is may have spread to away from the GTV and not a subregion of a GTV, such as draining lymph nodes.

Planning Target Volumes (PTV) and Internal Target Volume (ITV)

Region(s) to treat, including macroscopic disease and microscopic diseases with margins for delineation, motion and setup uncertainties.

Terminology for Irradiated Tissues

Clinical Treatment Region (CTR)

Region(s) to treat, including macroscopic disease and microscopic disease. The total disease burden with margins for delineation of uncertainties.

Dosimetric Treatment Region (DTR)

Region(s) of disease for which the mass and absorbed dose are estimated. The DTR is a subcategory of the CTR. The DTR is categorized into the Delineable Dosimetric Treatment Region(s) (DTR_D) and the Non-Delineable Dosimetric Treatment Region(s) (DTR_{ND}), depending on the possibility to perform patient-specific estimates of the tissue mass from images, and the level of uncertainty in the absorbed dose estimate. A region of disease included as a SR is generally also included among the DTRs.



Terminology for Irradiated Tissues

Terminology for Irradiated Tissues

Organs at Risk (OAR) and Remaining Volume at Risk (RVR)

Critical tissues that if irradiated could suffer significant morbidity or functional loss, and for which the mass and absorbed dose are estimated. The OAR is delineated for organs that may be acutely or chronically damaged by the radiation. The OAR may overlap with CTV or PTV. The RVR is the Patient Representation not included by the CTVs and OARs. The margin between the PTV and CTV would be considered part of the RVR if not otherwise cooccupied by part of an OAR.

Region at Risk (RAR)

Critical tissues that if irradiated could suffer significant morbidity or functional loss, and for which the mass and absorbed dose are estimated. The RAR is categorized into the Delineable Region(s) at Risk (RAR_D), the Non-Delineable Region(s) at Risk (RAR_{ND}) , and the Region at Risk for Secondary Effects (RAR_{SF}) . The categorization into RAR_{D} or RAR_{ND} is determined by the possibility to perform patientspecific estimates of the tissue mass from images, and the level of uncertainty in the absorbed dose estimate. The RAR_{SF} refers to irradiated body regions for which absorbed-dose estimates may be useful for estimating the long-term risk of stochastic effects. A normal tissue included as an SR is generally also included among the RARs.





Example of the application of the suggested nomenclature for a patient receiving ¹⁷⁷Lu-DOTATATE peptide receptor radionuclide therapy. The horizontal dashed lines indicate the limits of the field-of-view of the SPECT/CT scans that were acquired in parallel to these whole-body scans, representing the activity distribution at 1 h, 24 h, 96 h and 168 h after administration. Letters indicate the different types of regions as described to the right, also including the technique used for quantification of activity and mass.

Clinical Treatment Region (CTR) Neuroendocrine tumors

Localization Regions

Body regions that accumulate ¹⁷⁷Lu-DOTATATE, by the expression of somatostatin receptors or by other mechanisms, including tumors, liver, kidneys, spleen, small intestine, in some cases pituitary gland, salivary gland, thyroid.

SRDD: Left and right kidney (SPECT/CT)A: Tumors (SPECT/CT)E: Total Body (planar)

SR_{ND} **C**: Red bone marrow (whole-blood activity concentration)

DTR_D A: Tumors (CT or SPECT/CT)

DTR_{ND} B: Tumors that are either so small so that the relative standard deviation in the absorbed dose estimate is expected to be very high, or tumors that are located outside the SPECT/CT field of view.

RAR_D **D**: Left and right kidney (CT)

- **RAR**_{ND} **C**: Red bone marrow (mass based on patient weight and literature data)
- **RAR**_{SE} **E**: Total Body (patient weight)



Chapter 12 – Prescribing, Recording, and Reporting

General Principles

• As per previous ICRU reports, three reporting levels are identified for RPT. The requirements to achieve a given level depend on the radiopharmaceutical and therapeutic indication. Treating physicians and patients alike should seek the highest level that can be achieved within their constraints.



ICRU Reporting Levels

- Level 1 recommendations are the minimum standards for prescribing and reporting. Below these standards, any type of radiopharmaceutical therapy should not be performed.
- Level 2 recommendations apply for the prescribing and reporting state-of-the-art techniques so that the calculation is patient-specific and that it meets pre-specified uncertainty criteria. A complete Quality Assurance (QA) program is used to ensure that the prescribed treatment is accurately delivered. This translates into collecting the data required to calculate absorbed doses to the DTR and RAR. Depending upon the agent, clinical circumstances, and ability to accurately collect the needed data, this level should include adjustments to the prescribed activity based on the absorbed dose to the DTR and RAR.
- Level 3 recommendations are indicated for reporting research and novel developments. They are used for the development of new techniques and/or approaches for which reporting criteria are not yet standardized by the ICRU. The objective here is to develop and implement new techniques that may be implemented and refined in clinical trials to evaluate their applicability for widespread deployment as Level 2 recommendations.



Chapter 12 – Prescribing, Recording, and Reporting

ICRU Reporting Levels – Example

Radio- pharmaceutical therapy	Treatment indication	Posology	Prospective dosimetry (pre-treatment)	Verification dosimetry (post-treatment)	Treatment driving quantity (RAR or DTR)
¹⁷⁷ Lu DOTATATE	Neuroendocrine tumors	 L1: Administered activity and amino acids as per package insert L2: D(lesions) and RAR L3: TCP/NTCP- optimization 	L1: None L2: ¹⁷⁷ Lu DOTATATE quantitative imaging for treatment fractions following the first L2: ⁶⁸ Ga DOTATATE may be used for mass estimation L3: ⁶⁸ Ga DOTATATE used for mass estimation	L1: None L2: ¹⁷⁷ Lu DOTATATE quantitative imaging and dosimetry for one, several, or preferably all treatment fractions L3: ¹⁷⁷ Lu DOTATATE quantitative imaging and dosimetry for all treatment fractions	L1: None L2: RARD = kidneys RARND = bone marrow L3: DTR = tumors

Posology - the part of medicine concerned with dosage



Chapter 13 – Future Areas of Study in RPT

General Principles

- Absorbed-dose driven implementation and treatment planning of RPT, as outlined in this report, will be adopted only if such treatment planning is shown to provide a long-term survival advantage over the more expedient approach of adopting a chemotherapy dosing paradigm. To date, studies demonstrating the advantages of dosimetry and treatment planning in RPT have not been conducted with the level of rigor and transparency required to change practice standards. Recommendations are:
- 1. Standardized, well-validated quantitative imaging and dosimetry techniques
- 2. Methods that reduce the logistical burden on patients and that are easy to implement while also preserving accuracy.
- 3. Reporting that includes an assessment of the accuracy of the calculation (e.g., by providing the standard deviation of the reported absorbed dose result).



Chapter 13 – Future Areas of Study in RPT

General Principles

- The following additional areas are important for the future progress of the field, especially as interest in alpha-particle emitter RPT continues to increase. Recommendations are:
- 1. Research to better elucidate the relationship between absorbed dose nonuniformity at the microscale and biologic effect for both normal tissues and tumors.
- 2. Bioeffect modeling that incorporates the nonuniformity at the microscale, dose-rate effects, and high-LET effects.



Thank you for your attention. Would be happy to entertain any questions!







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