Universitätsklinikum Würzburg

Dosimetry in Diagnostic and Therapeutic Nuclear Medicine

M. Lassmann

Klinik und Poliklinik für Nuklearmedizin
Direktor: Prof. Dr. A. Buck

Contents

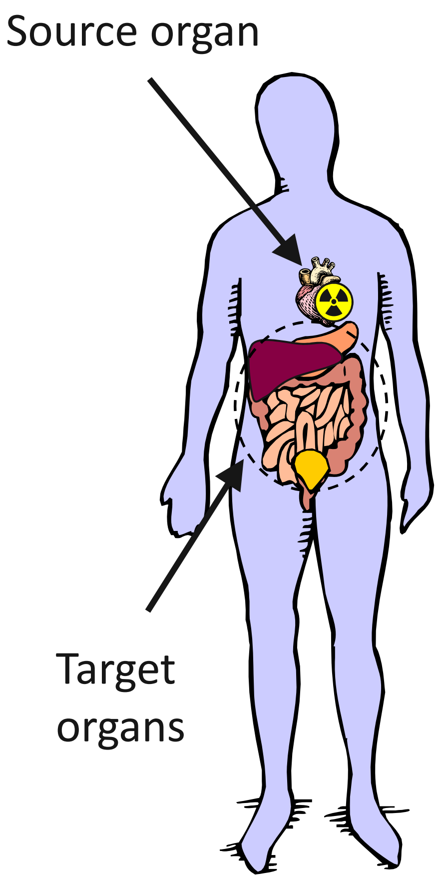
- Introduction
- Basic Principles
  - The MIRD Concept
  - Three Steps to Calculate Absorbed Doses

- Applying the MIRD Concept
  - Diagnostics
  - Treatment of Differentiated Thyroid Cancer
  - Treatment of Neuroendocrine Tumors
  - SIRT

- Conclusion

Fundamentals of Nuclear Medicine Dosimetry

- The administered activity distributes in the body
- Based on cellular functions and physiology, it accumulates in individual organs in a different way (biodistribution and biokinetics)
- Source organs irradiate target organs, self-irradiation of organs is also possible
- For assessing radiation-related risks, the absorbed dose in the individual organs needs to be calculated
- For calculating absorbed dose, a formalism called MIRD*-Scheme was developed in 1976 (summing over all organ contributions)



* *M*edical *I*nternal *R*adiation *D*ose - group of the Society of Nuclear Medicine, USA

Isotopes used for Therapy

Radio-nuclide	Halflife (h)	β_{max} (MeV)	γ (keV)	Max. range (mm)
I-131	192	0.61	364	2.0
Y-90	64	2.3	-	12
Lu-177	161	0.50	208	1.5
Ra-223	274	α		

Paradigm of Targeted Molecular Radiotherapy:

Optimisation of the efficacy by minimising the damage to normal organs/tissues („Safety“)

Therapy Modalities

Metabolic active radiopharmaceuticals

- Radioiodine Therapy of Thyroid Diseases (benign/malignant)
- Bone Pain Palliative Treatment of Bone Metastases

Specifically binding radiopharmaceuticals

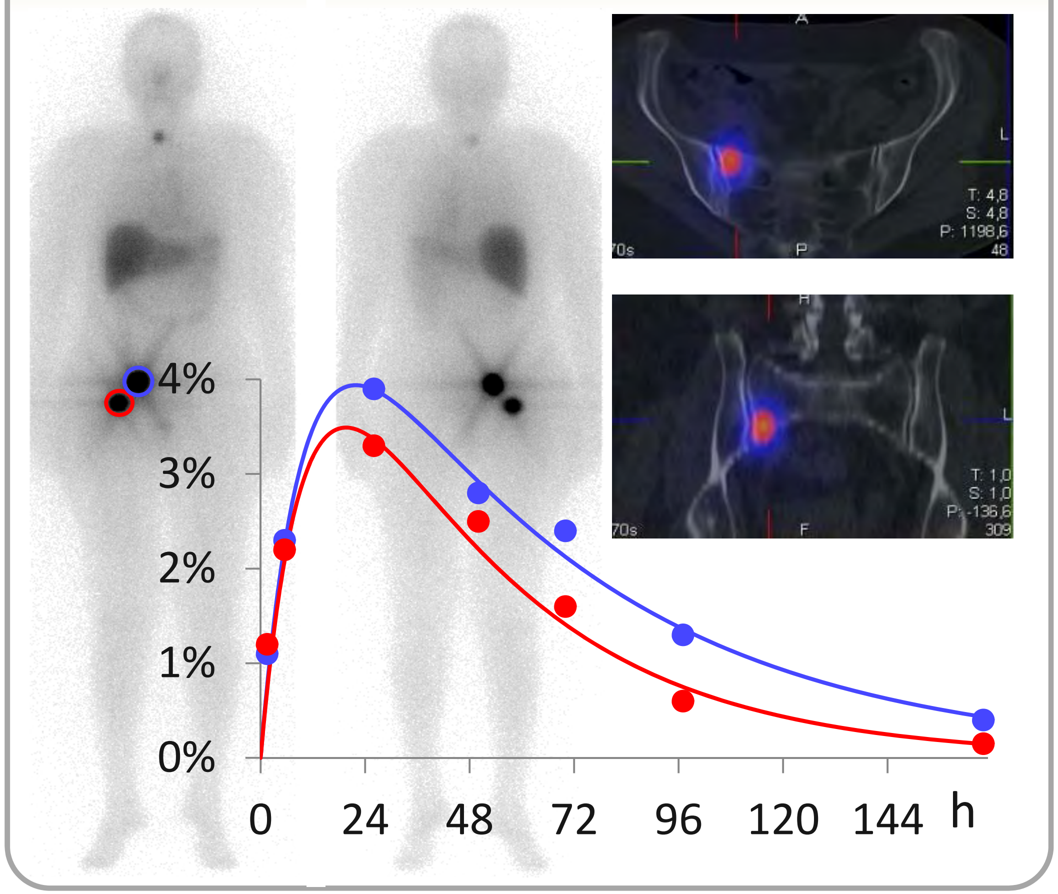
- Radiopeptide therapy (addressing specific antigens or receptors)
- Treatment of lymphoma using antibodies

Locoregional therapies

- Selective Internal radiotherapy
- Radiosynoviorthesis

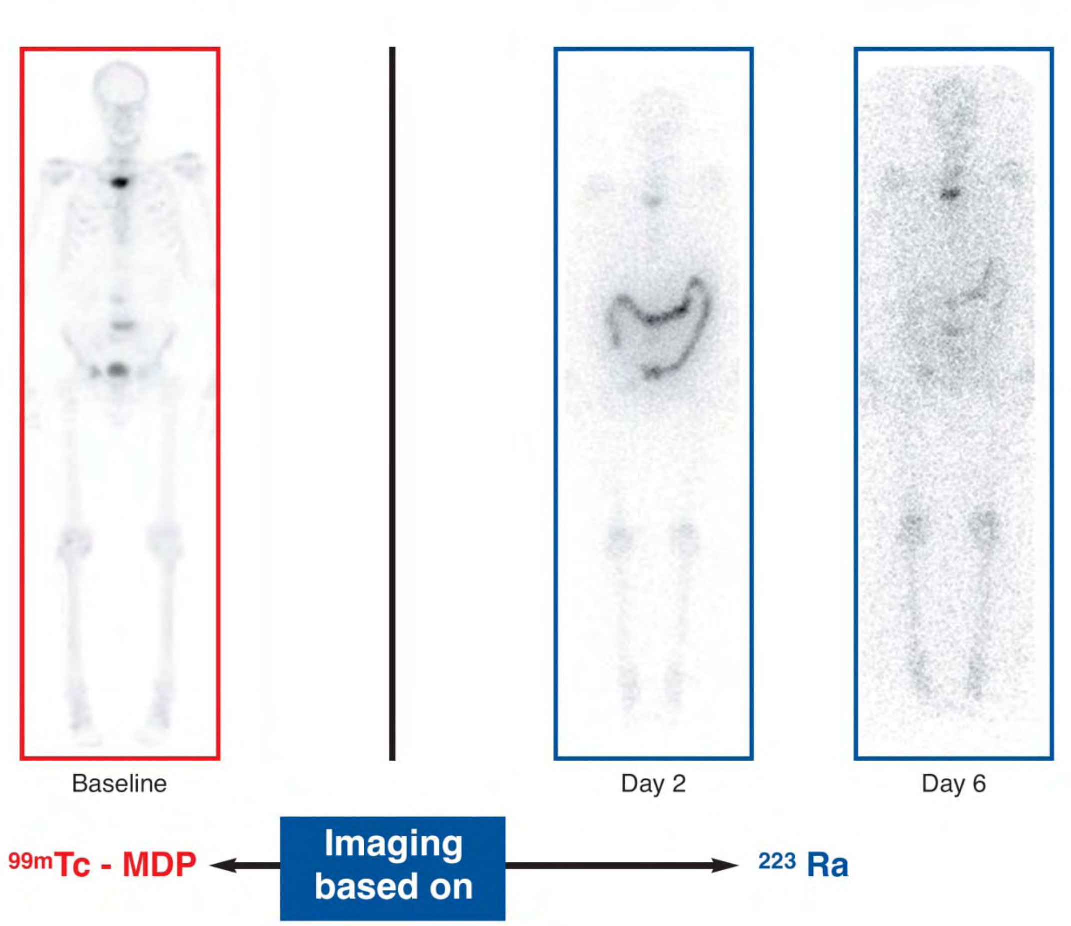
Radioiodine Therapy of Thyroid Cancer

$$\mathrm{D}(\mathrm{r}_\mathrm{T}) = \sum_S \Bigg(\Big(\int A(r_S, t)\,dt \cdot \mathrm{S}(\mathrm{r}_\mathrm{T} \leftarrow \mathrm{r}_\mathrm{S}) \Bigg)$$



Title:
Z Med Phys
December 2011

Palliation of Bone Metastases



Patients with painful osseous metastases and reduced quality of life

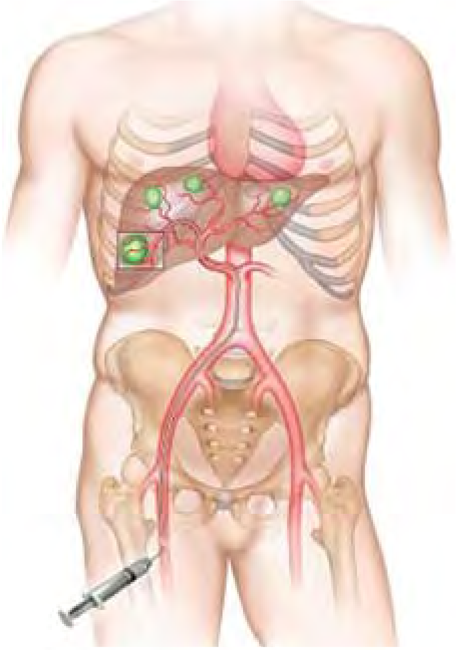
Increased uptake in places of augmented bone metabolism

Sparing of sound bone tissue

Alpharadin, a novel, targeted approach for treatment of bone metastases from CRPC

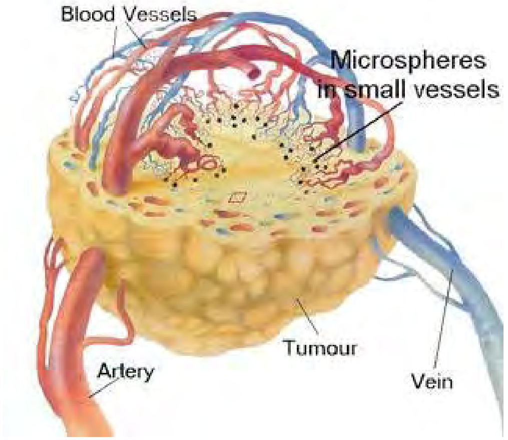
Lewington et al, Poster@ASCO 2011

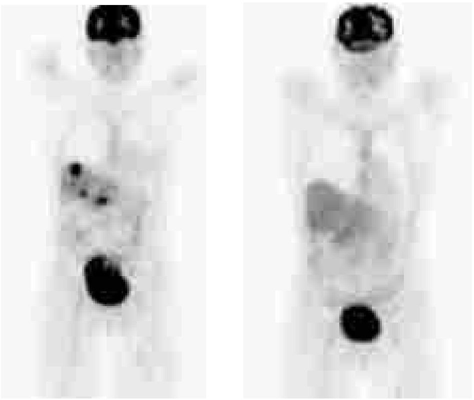
Example: Selective Internal Radiotherapy



Transarterial embolization of radioactive labeled microspheres (Y-90)

Highly selective tumor uptake by intra-arterial administration of the particles through the a. hepatica





http://nuk.klinikum.uni-muenchen.de/therapie/014_ther_sirt.php
http://www.sec.gov/Archives/edgar/data/873364/000110465903001888/j7431_ex99d1.htm

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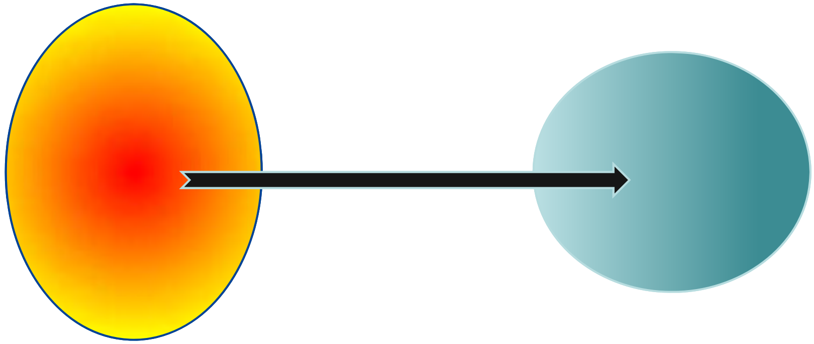
MIRD Formalism: Volume Generalisation



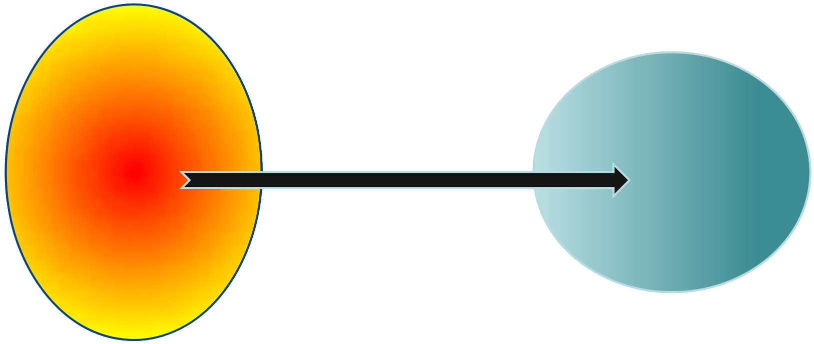
Source h

Target k

$$\overline{D}(k \leftarrow h) = \frac{E}{m_k} = \frac{\phi(k \leftarrow h) \cdot E_0}{m_k} = \Phi(k \leftarrow h) \cdot E_0$$

$\overline{D}$ *mean* absorbed dose over target volume

Non-penetrating Radiation



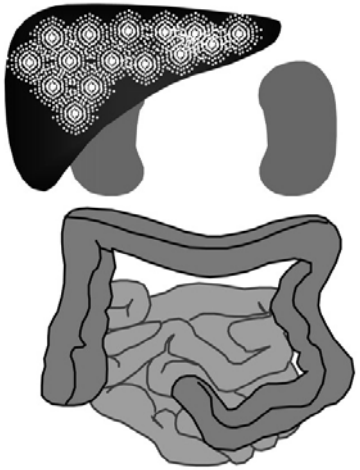
Source h

Target k

$$\phi_i(k \leftarrow h) = 0 \; if \;\; k \neq h$$

$$\phi_i(k \leftarrow h) = 1 \; if \;\; k = h$$

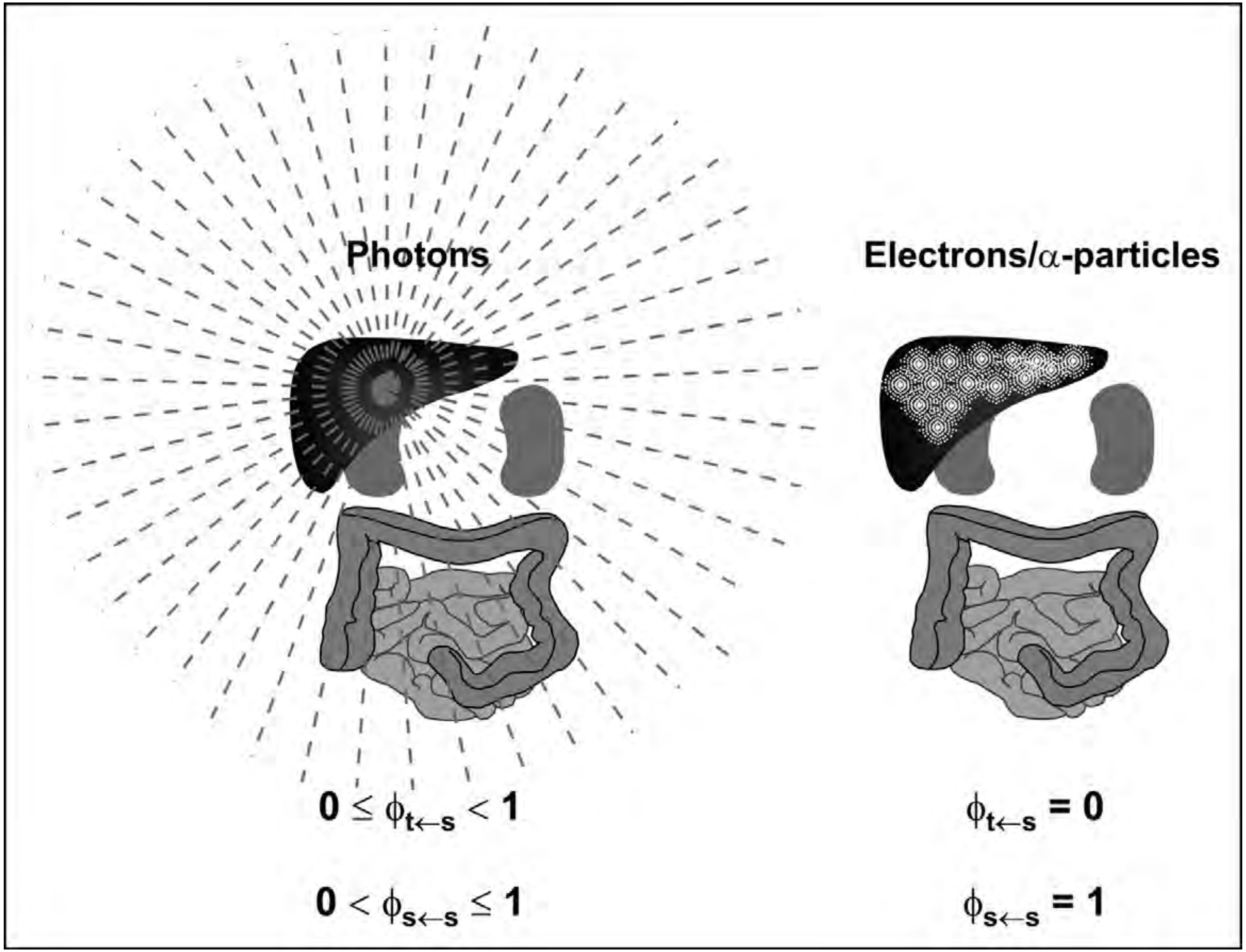
Electrons/α-particles



$$\overline{D}(k \leftarrow k) = \frac{\phi(k \leftarrow k) \cdot E_0}{m_k} = \frac{E_0}{m_k}$$

$$\overline{D}(k \leftarrow h) = 0$$

Depends on: organ size & particle range


Photons
Electrons/α-particles
$0 \le \phi_{t \leftarrow s} < 1$
$0 < \phi_{s \leftarrow s} \le 1$
$\phi_{t \leftarrow s} = 0$
$\phi_{s \leftarrow s} = 1$

Radionuclide generalisation

The dose rate is the sum of all contributions (all type i radiation)

$$\overline{\dot{D}}(t)_{(k\leftarrow h)} = K \cdot A_h(t) \cdot \sum_i n_i E_i \cdot \Phi_i(k \leftarrow h)$$

Integration over Time

Take into account the time during which irradiation takes place...

$$\overline{D}_{(k\leftarrow h)} = \int_{t_1}^{t_2} \overline{\dot{D}}(t)_{(k\leftarrow h)}\,dt$$

Therefore:

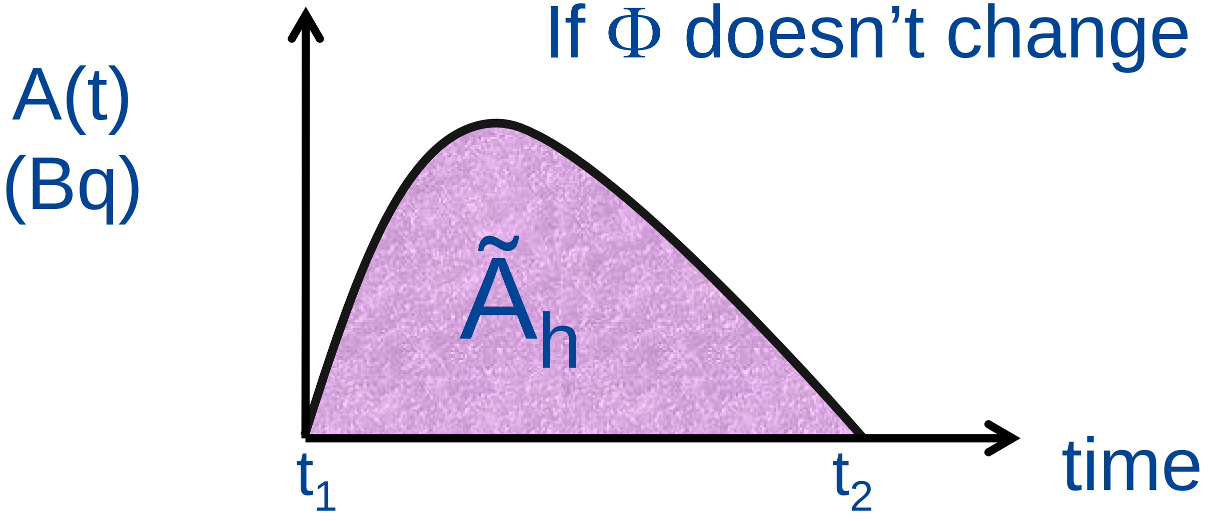
$$\overline{D}_{(k\leftarrow h)} = \int_{t_1}^{t_2} K \cdot A_h(t) \cdot \sum_i n_i E_i \cdot \Phi_i\left(k \leftarrow h\right) dt$$

$\overline{D}_{(k\leftarrow h)}$ is the mean absorbed dose (Gy) in target k from source h

Integration over Time (2)

$$\overline{D}_{(k\leftarrow h)} = K\cdot\sum_{i} n_i E_i \cdot \Phi_i(k\leftarrow h)\cdot\int_{t_1}^{t_2} A_h(t)dt$$

If Φ doesn't change with time!



$$\tilde{A}_h = \int A_h(t)dt$$

Cumulated activity (Bq.s or µCi.h)
'time integral of the activity'

Cumulated activity

$$\tilde{A}_h = \int A_h(t)dt$$

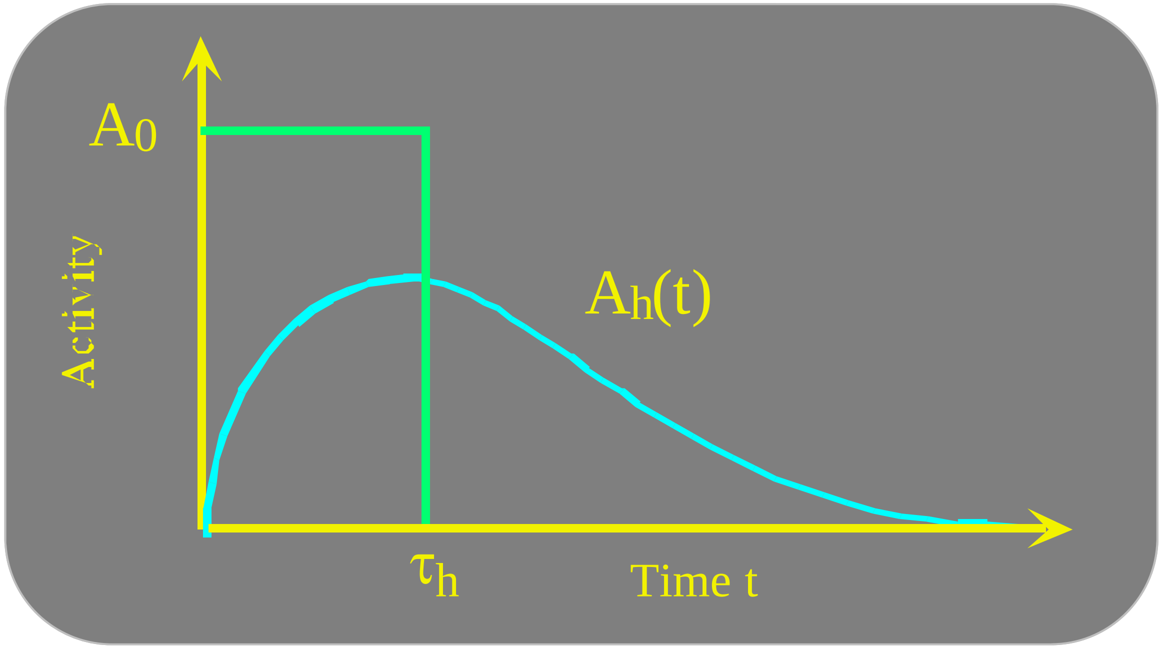
$\tilde{A}_h$ represents the total number of nuclear transitions occurring in source h

Usually: lower limit: 0
upper limit: ∞

$$\tilde{A}_h = \int_0^\infty A_h(t)dt$$

$\tilde{A}_h$ is calculated from biologic data: pharmacokinetics
estimated graphically, numerically, …

Residence time: τ_h



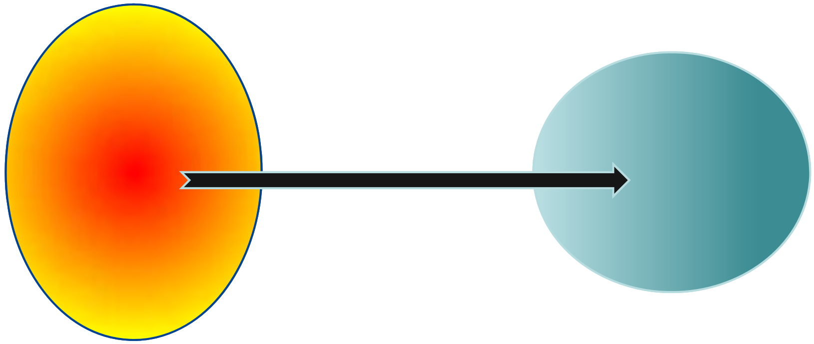
$$\tilde{A}_h = \int A_h(t)dt$$

$$\tau_h = \frac{\tilde{A}_h}{A_0}$$

$\tilde{A}_h$ in Bq.s
A_0 in Bq
} τ_h in s

A_0 is the injected activity

MIRD simplified equation

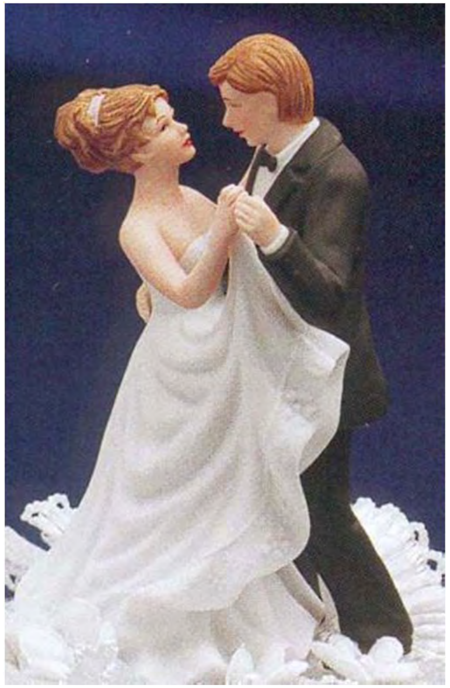


Source h

Target k

$$\overline{D}_{(k\leftarrow h)} = \tilde{A}_h \cdot S_{(k\leftarrow h)}$$

$$\frac{\overline{D}_{(k\leftarrow h)}}{A_0} = \tau_h \cdot S_{(k\leftarrow h)}$$



Internal dose estimates – “marriage” of physical and biological quantities

- Biology – distribution and kinetics
- Physics – energy deposition patterns

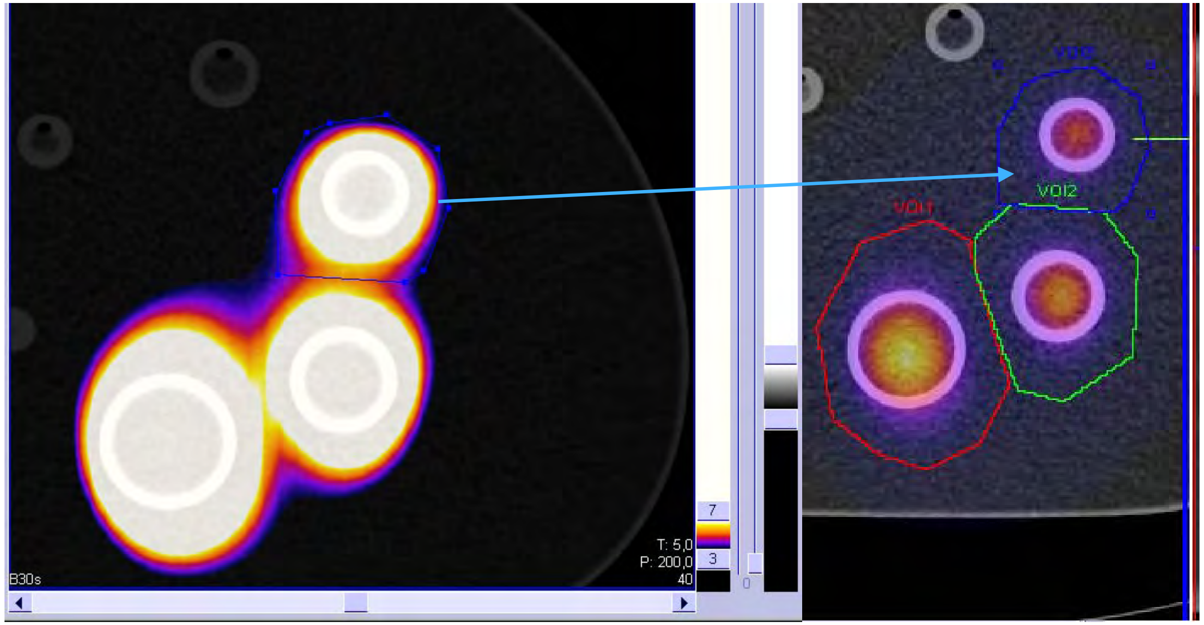
The Three Steps for Internal Dosimetry

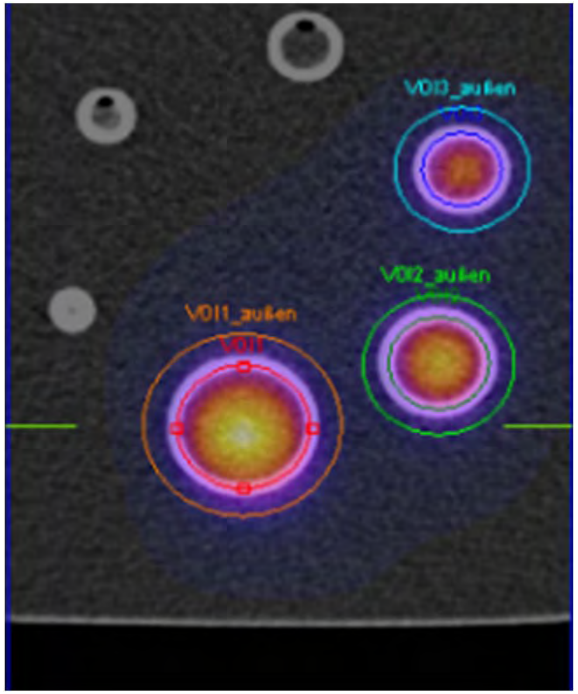
- Quantitative Imaging

Calibration – measurement set-up

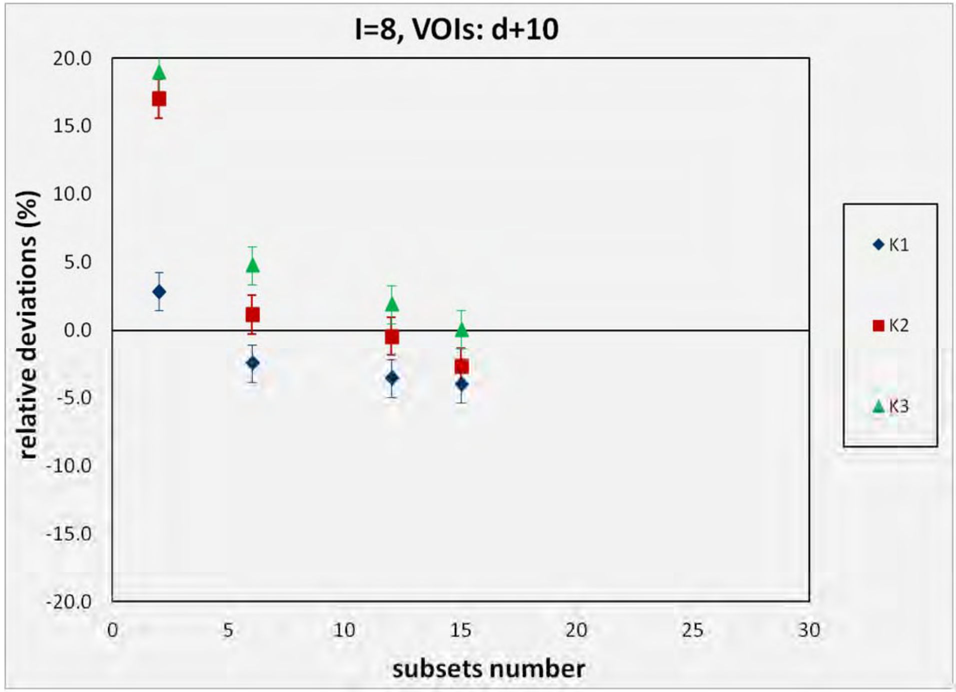
SPECT/CT: Symbia T2 (Siemens)

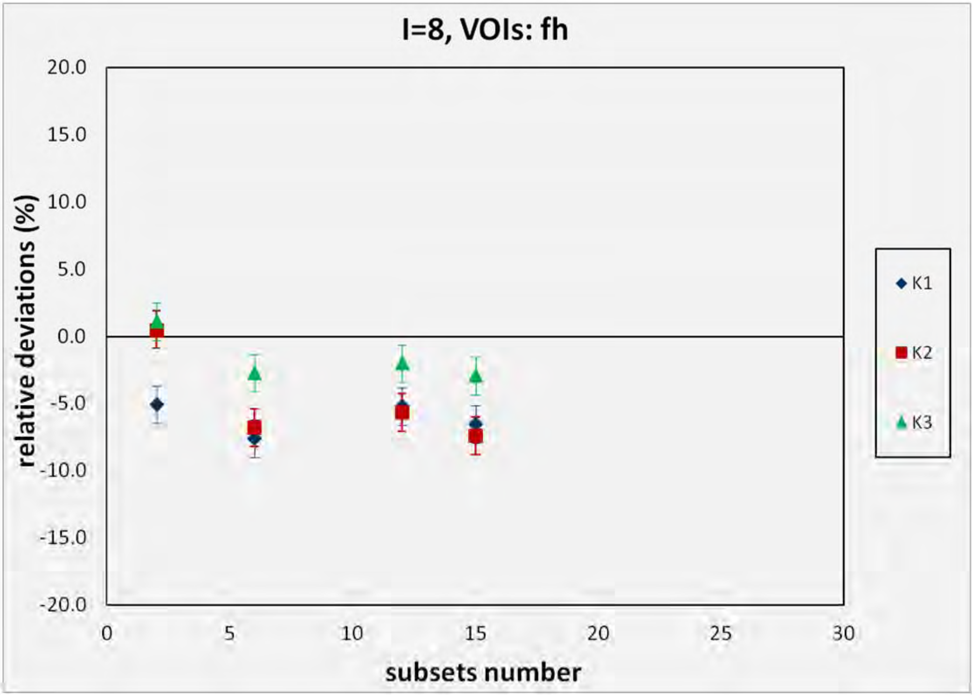
Calibration and quantification





Calibration – Reconstruction





The Three Steps for Internal Dosimetry

- Quantitative Imaging

- Integration of the Time-Activity Curve

Example - PRRT

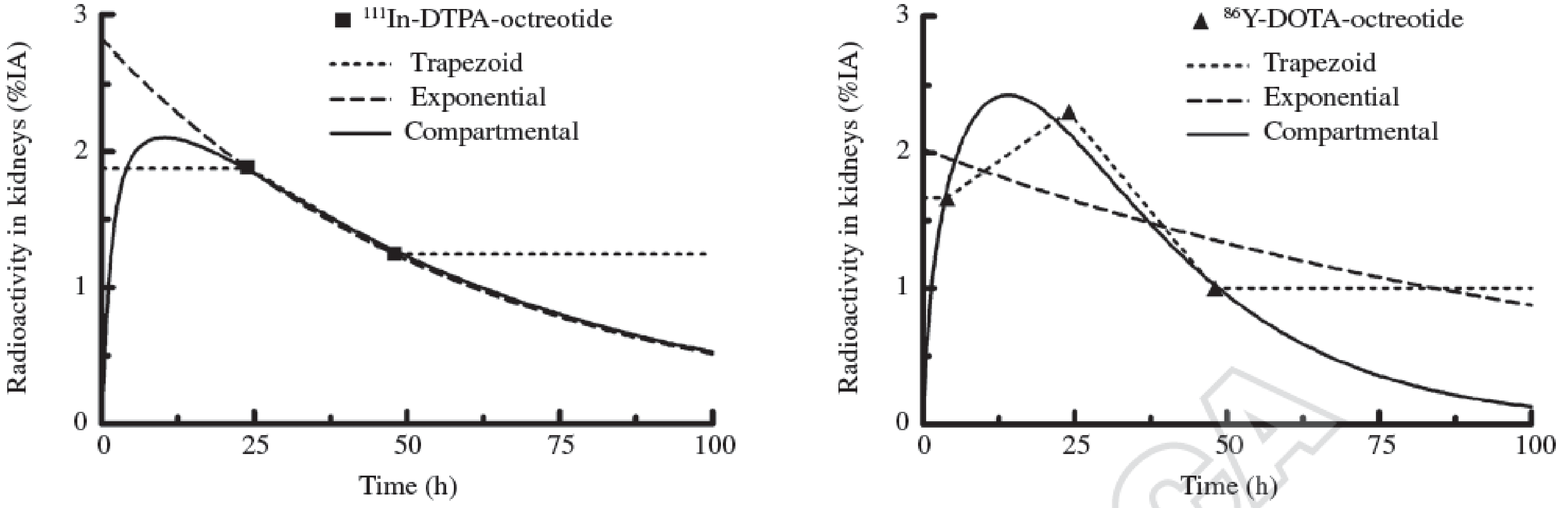
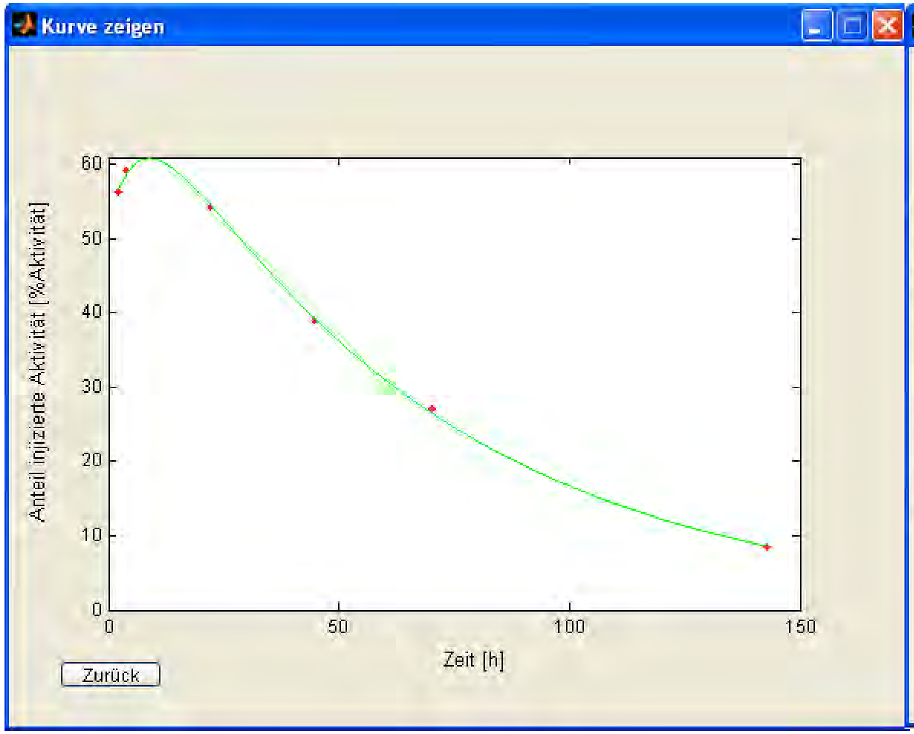


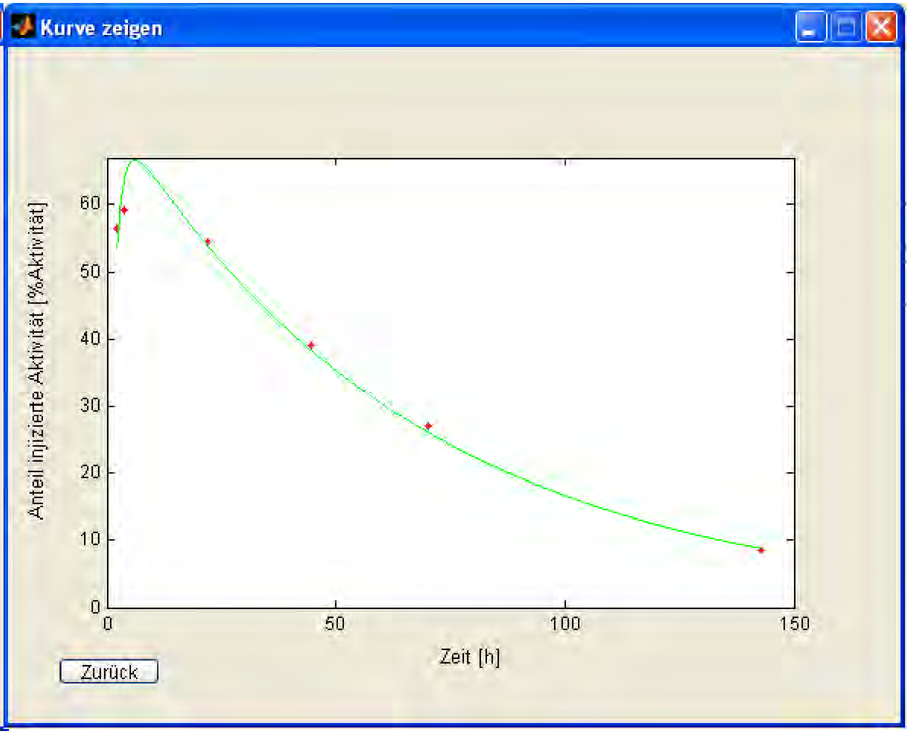
Figure 1.—Radioactivity uptake in the kidneys of a patient, injected with ^{111}In-DTPA-octreotide (left graph) and with ^{86}Y-DOTA-octreotide (right graph). Three curve fitting methods were used for establishing the time-activity curve: the trapezoid method, a single exponential and by compartmental modelling.

Konijnenberg M. From imaging to dosimetry and biological effects. Q J Nucl Med Mol Imaging 2011; 55: 44-56.

Example: Radioimmunotherapy

$$f_1(t) = A_1 \cdot e^{-(\lambda_{phys}+\lambda_1)\cdot t} + A_2 \cdot e^{-(\lambda_{phys}+\lambda_2)\cdot t} \qquad f_2(t) = A_1 \cdot \left(e^{-(\lambda_{phys}+\lambda_1)\cdot t} - e^{-(\lambda_{phys}+\lambda_2)\cdot t}\right)$$





NukDos

Universitätsklinikum Würzburg

Bundesamt für Strahlenschutz

universität ulm

Medizinische Fakultät Mannheim
der Universität Heidelberg
Universitätsklinikum Mannheim

Molecular radiotherapy: The NUKFIT software for time-integrated activity coefficient calculation

P. Kletting, S. Schimmel, H. A. Kestler, H. Hänscheid, M. Luster, M. Fernández, J.H. Bröer, D. Nosske, M. Lassmann, G. Glatting

This work is financed by the BMBF (AZ: 01EZ1130)

Med. Phys. 2013

Bundesministerium
für Bildung
und Forschung

Klinik und Poliklinik für Nuklearmedizin
Direktor: Prof. Dr. A. Buck

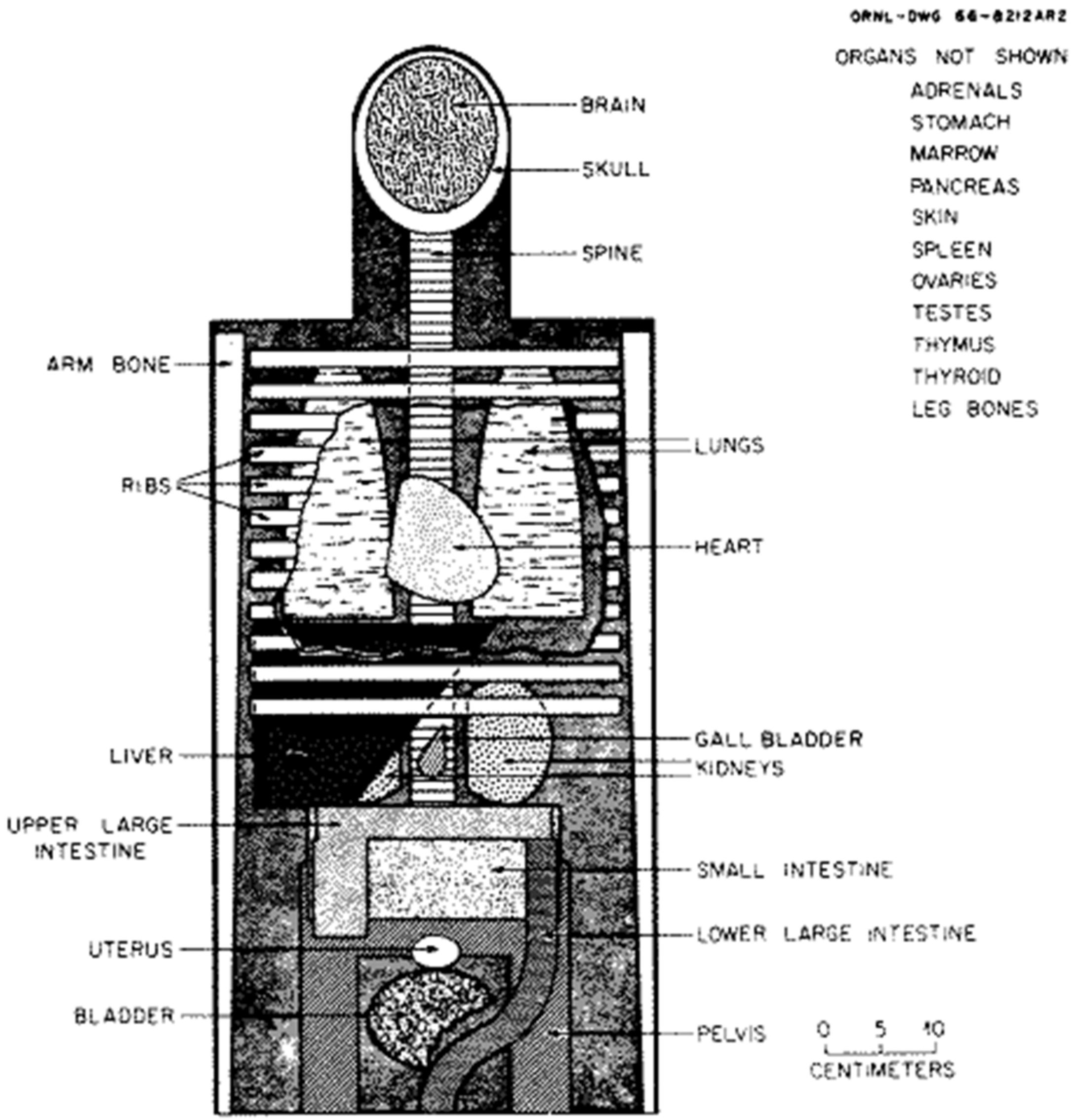
The Three Steps for Internal Dosimetry

- Quantitative Imaging
- Integration of the Time-Activity Curve
- Determination of the S-Values

Applying the MIRD Formalism: Diagnostics

$\tilde{A}_h$	$S(k \leftarrow h)$	$\overline{D}_{(k \leftarrow h)}$
Group	model	model
Specific	Model ± adjusted	Model ± realistic
Specific	Specific	Specific

$\tilde{A}_h$ from animal studies, healthy volunteers, etc.
S from anthropomorphic phantoms
Model based dosimetry: IRCP, MIRD DER



Anthropomorphic phantoms:

Human anatomy representation:
simplified organ shapes
realistic density

Absorbed fractions calculation:
Monte-Carlo
Analytic

Gives an idea of the delivered absorbed dose for ≠ radionuclides

MIRD pamphlets

+

MIRD DER: dose estimate reports

≠ radiopharmaceuticals
≠ biokinetics

Applying the MIRD Formalism

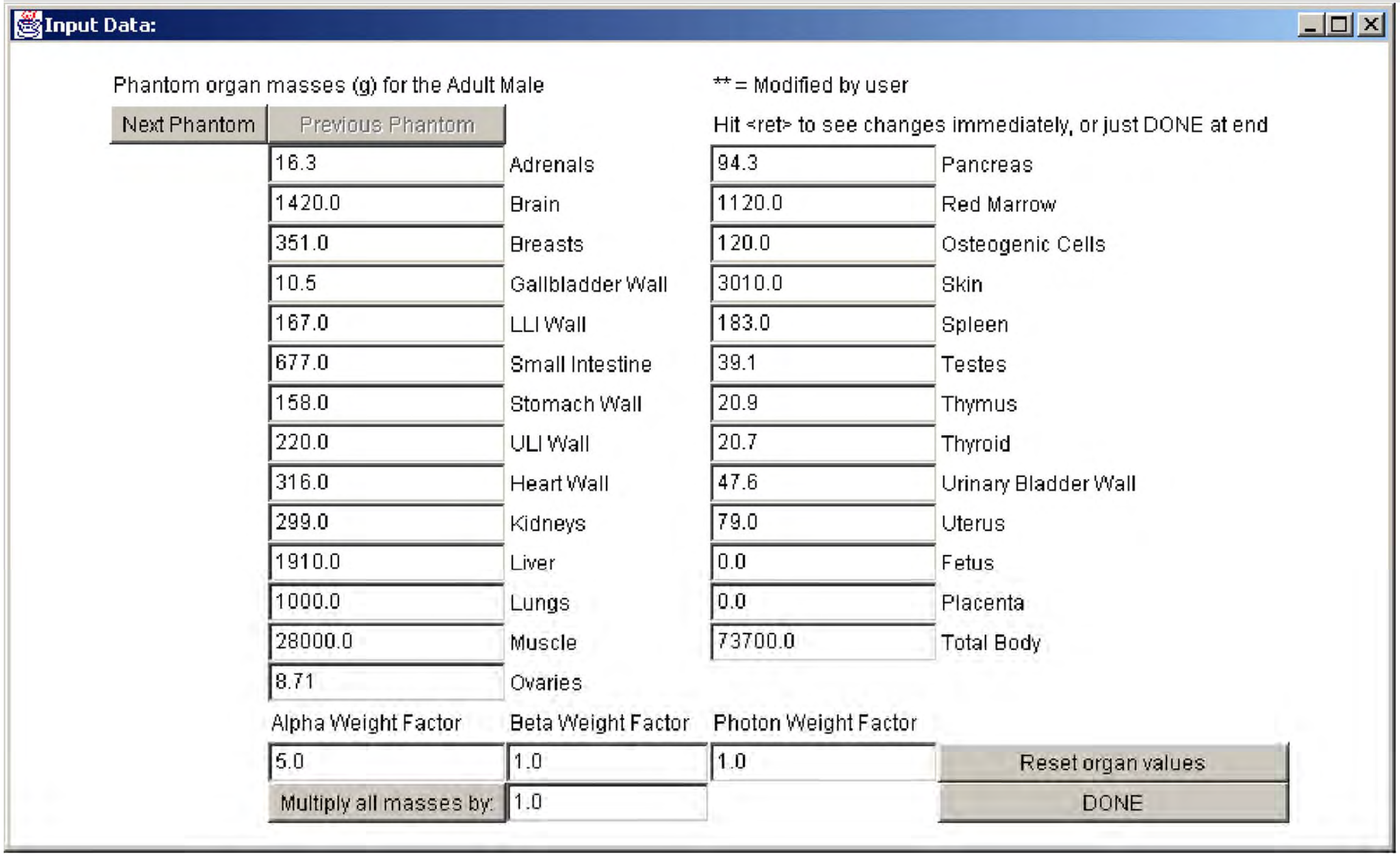
$\tilde{A}_h$	$S(k \leftarrow h)$	$\overline{D}_{(k \leftarrow h)}$
Group	model	model
Specific	Model ± adjusted	Model ± realistic
Specific	Specific	Specific

Patient-specific $\tilde{A}_h$ determination.

S from « realistic » anthropomorphic phantoms

« Realistic » Model based dosimetry: most frequent

Olinda mass adjustment module



Phantom organ masses (g) for the Adult Male

** = Modified by user

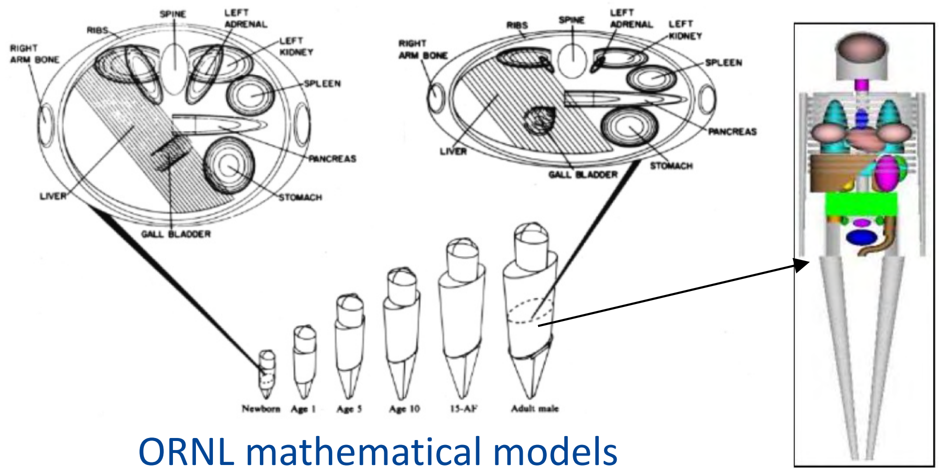
Hit <ret> to see changes immediately, or just DONE at end

16.3	Adrenals	94.3	Pancreas
1420.0	Brain	1120.0	Red Marrow
351.0	Breasts	120.0	Osteogenic Cells
10.5	Gallbladder Wall	3010.0	Skin
167.0	LLI Wall	183.0	Spleen
677.0	Small Intestine	39.1	Testes
158.0	Stomach Wall	20.9	Thymus
220.0	ULI Wall	20.7	Thyroid
316.0	Heart Wall	47.6	Urinary Bladder Wall
299.0	Kidneys	79.0	Uterus
1910.0	Liver	0.0	Fetus
1000.0	Lungs	0.0	Placenta
28000.0	Muscle	73700.0	Total Body
8.71	Ovaries		

Alpha Weight Factor	Beta Weight Factor	Photon Weight Factor
5.0	1.0	1.0

Multiply all masses by: 1.0

Mass Adjustment:



ORNL mathematical models

(ORNL/8381)

Standard S values

For SELF Irradiation Only

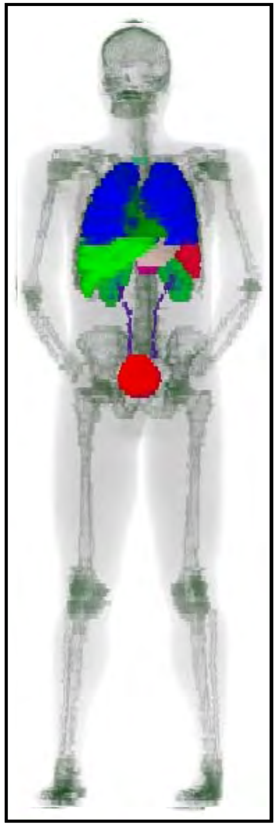
$$S_{r\leftarrow r}(patient) = S_{r\leftarrow r}(standard)\cdot \frac{Mass_r(standard)}{Mass_r(specific)}$$

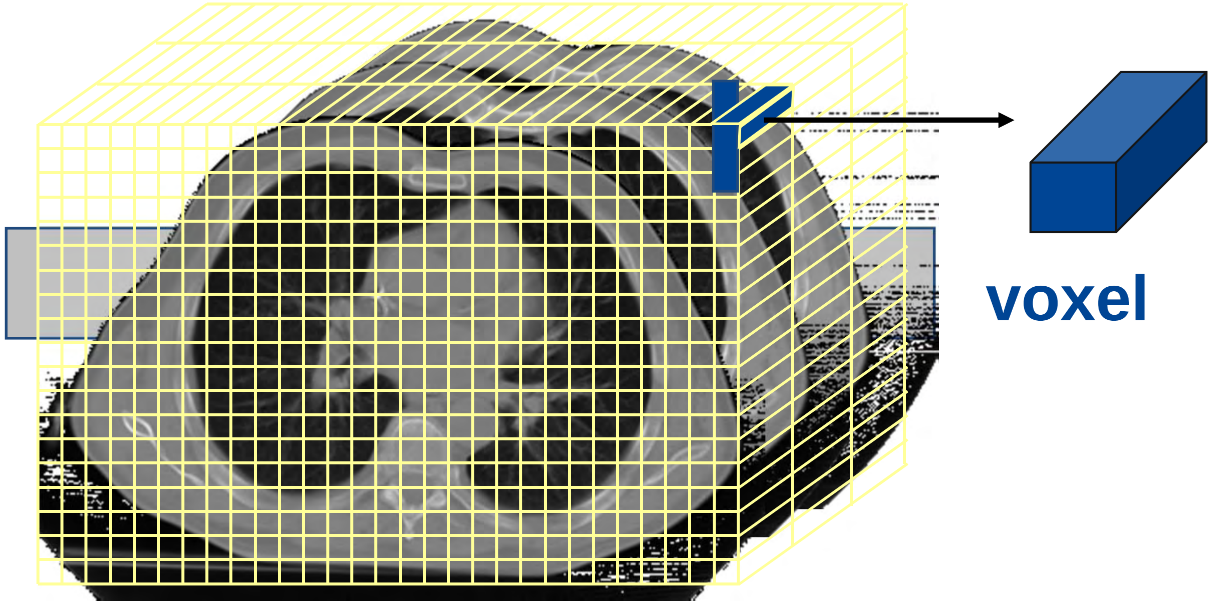
Applying the MIRD Formalism

$\tilde{A}_h$	$S(k \leftarrow h)$	$\overline{D}_{(k \leftarrow h)}$
Group	model	model
Specific	Model ± adjusted	Model ± realistic
Specific	Specific	Specific

Patient-specific $\tilde{A}_h$ determination.
Patient-specific S factor determination
Patient-specific dosimetry: therapy

Patient specific dosimetry



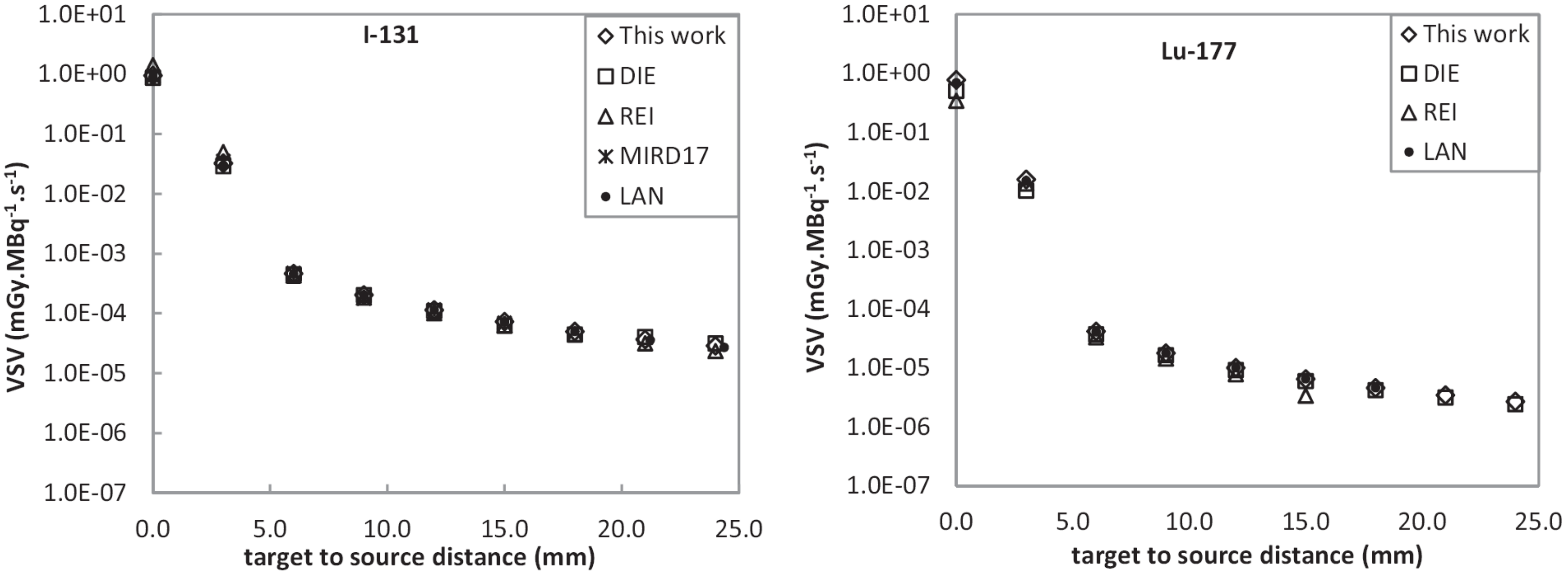


Specific S values

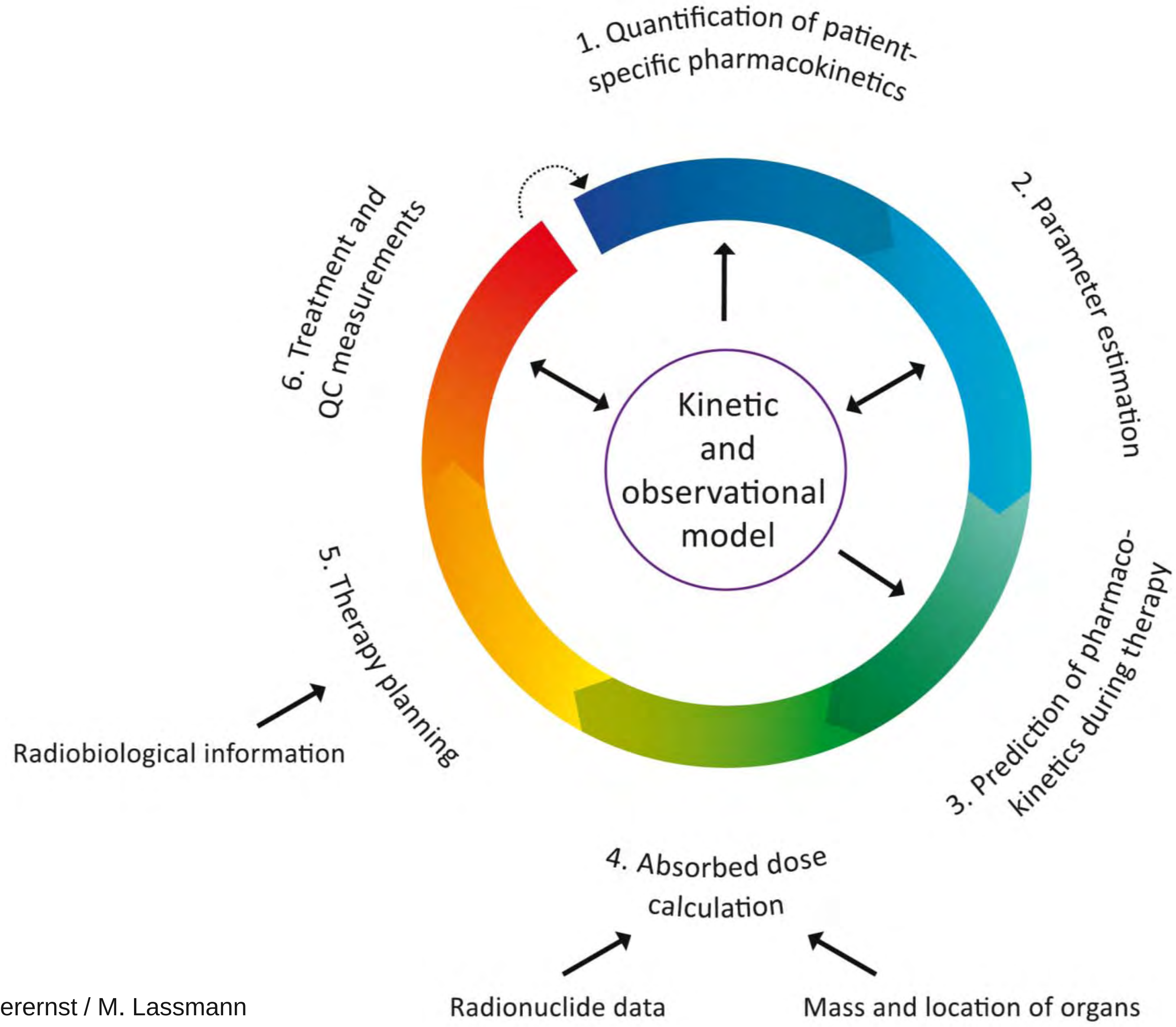
A fast method for rescaling voxel S values for arbitrary voxel sizes in targeted radionuclide therapy from a single Monte Carlo calculation

M. Fernández, H. Hänscheid, T. Mauxion, M. Bardiès, P. Kletting,
G. Glatting, M. Lassmann

Med. Phys. 2013



Dosimetry Setup



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The NUKDOS Software for Dosimetry in Molecular Radiotherapy

Peter Kletting[1], Sebastian Schimmel[1], Heribert Hänscheid[2], Maria M. Fernandez[2], Jörn H. Bröer[3], Dietmar Noßke[3], Michael Lassmann[2] and Gerhard Glatting[4]

[1]Klinik für Nuklearmedizin, Universität Ulm; [2]Klinik für Nuklearmedizin, Universität Würzburg; [3]Bundesamt für Strahlenschutz, Fachbereich Strahlenschutz und Gesundheit; [4]Medizinische Strahlenphysik/Strahlenschutz, Medizinische Fakultät Mannheim, Universität Heidelberg

EANM Congress 2013

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$\tilde{A}_h$ from animal studies, healthy volunteers, etc.
S from anthropomorphic phantoms
Model based dosimetry: IRCP, MIRD DER

Diagnostic nuclear medicine

- Low amounts of radiation delivered (stochastic effects)
- Dosimetry: for pre-marketing authorization (EMA, FDA) to establish posology/Diagnostic Reference Levels (DRLs)
- ICRP recommendations
- EANM pediatric dosage card

Effective Dose E

- Introduced by ICRP 60 in 1991
- Effective dose is a protection quantity

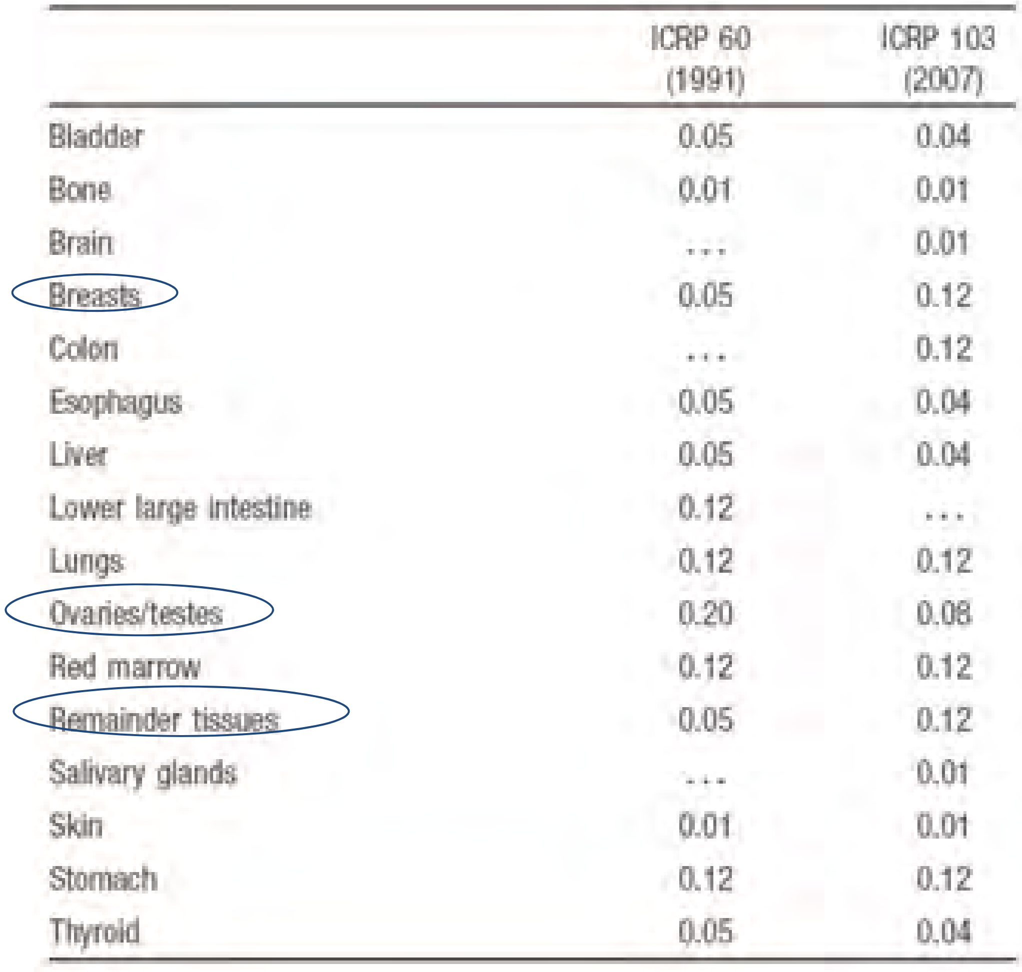
$$E = \sum_T w_T H_T$$

  - Ö$_7$: tissue weighting factor, +$_7$: equivalent dose in organ 7
  - +$_{7\#}$: organ absorbed dose weighted by a radiation weighting factor

- Related to the probability of health detriment to an adult reference person due to stochastic effects from exposure to low doses of ionizing radiation
- To compare different diagnostic procedures, or similar procedures in different hospitals and countries
- Not for individual dose and risk assessment
- This concept is problematic for the use in children

Effective Dose: Changes in ICRP 103

- ICRP defined new tissue weighting factors in their 2007 report (ICRP 103)
- The most significant changes are for breast tissue, gonads and the remainder organs



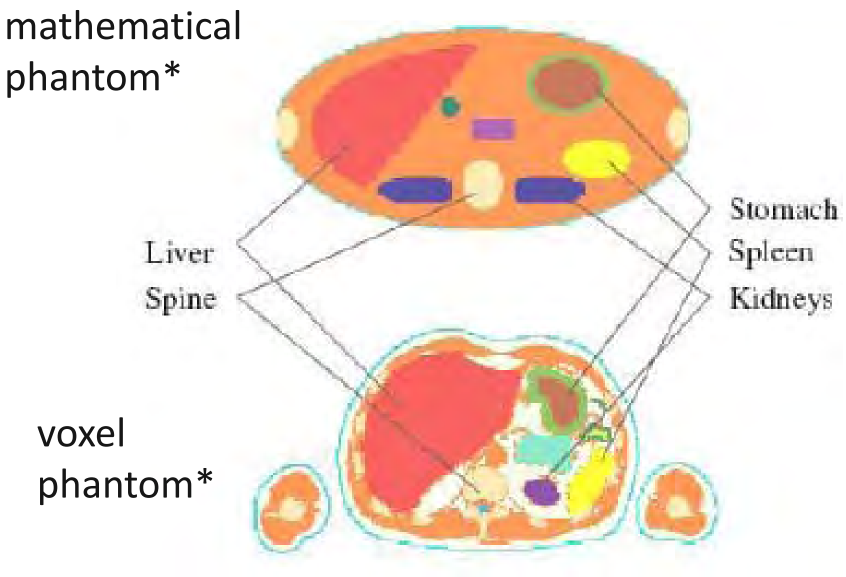
	ICRP 60 (1991)	ICRP 103 (2007)
Bladder	0.05	0.04
Bone	0.01	0.01
Brain	. . .	0.01
Breasts	0.05	0.12
Colon	. . .	0.12
Esophagus	0.05	0.04
Liver	0.05	0.04
Lower large intestine	0.12	. . .
Lungs	0.12	0.12
Ovaries/testes	0.20	0.08
Red marrow	0.12	0.12
Remainder tissues	0.05	0.12
Salivary glands	. . .	0.01
Skin	0.01	0.01
Stomach	0.12	0.12
Thyroid	0.05	0.04

Ann ICRP 2007, 37 (2-4)

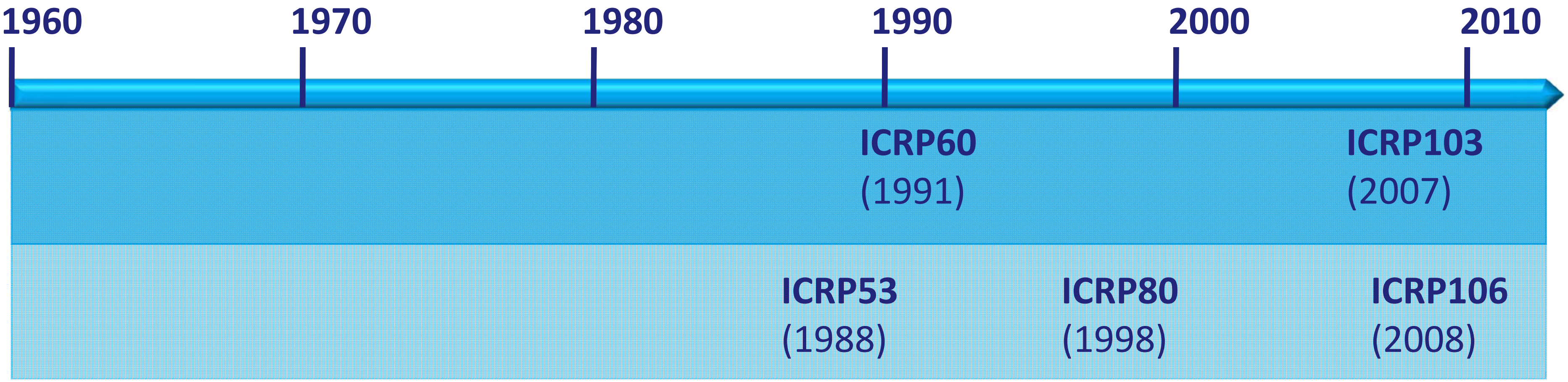
Effective Dose: Changes in ICRP 103

- ICRP clearly defined more realistic female and male voxel phantoms
- Calculate organ absorbed doses for males and females separately and calculate the arithmetic mean of the equivalent dose

- The S-values have not yet been recalculated with the new models, therefore the new formalism of ICRP 103 cannot be applied to nuclear medicine at present



Evolution: ICRP reports



1960 1970 1980 1990 2000 2010

ICRP60 (1991)

ICRP103 (2007)

ICRP53 (1988)

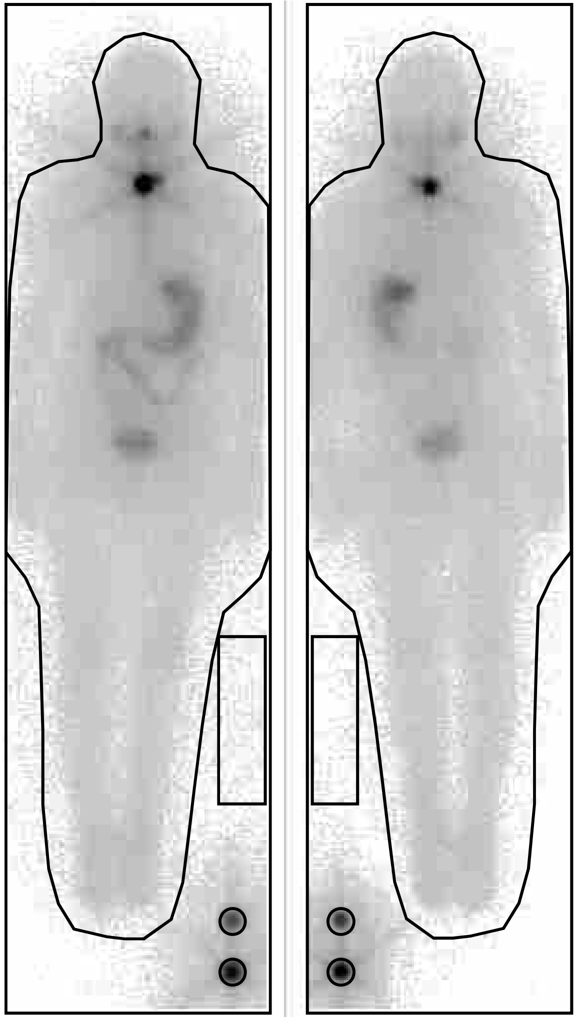
ICRP80 (1998)

ICRP106 (2008)

"Radiation dose to patients from radiopharmaceuticals"

- 1988 ICRP Publication 53. Ann. ICRP 18 (1-4)
- 1993 Addendum 1 to ICRP Publication 53. Ann. ICRP 22(3)
- 1998 Addendum 2 to ICRP Publication 53. Ann. ICRP 28 (3)
- 2008 Addendum 3 to ICRP Publication 53. Ann. ICRP 38 (1-2)

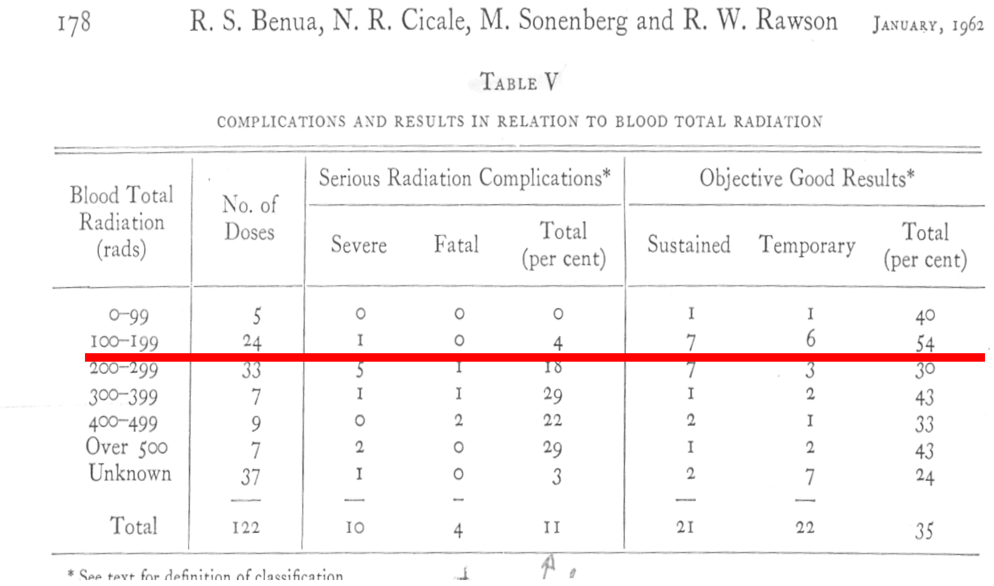
Example I: Absorbed Dose to the Blood in DTC Patients



Hänscheid, Lassmann… JNM 2006

- ➢ Surrogate for the Bone Marrow Dose
- ➢ Aim: Maximising the absorbed dose to the tumor while avoiding myelotoxicity

(< 2 Gy no bone marrow suppression
Benua 1962)



178 R. S. Benua, N. R. Cicale, M. Sonenberg and R. W. Rawson JANUARY, 1962

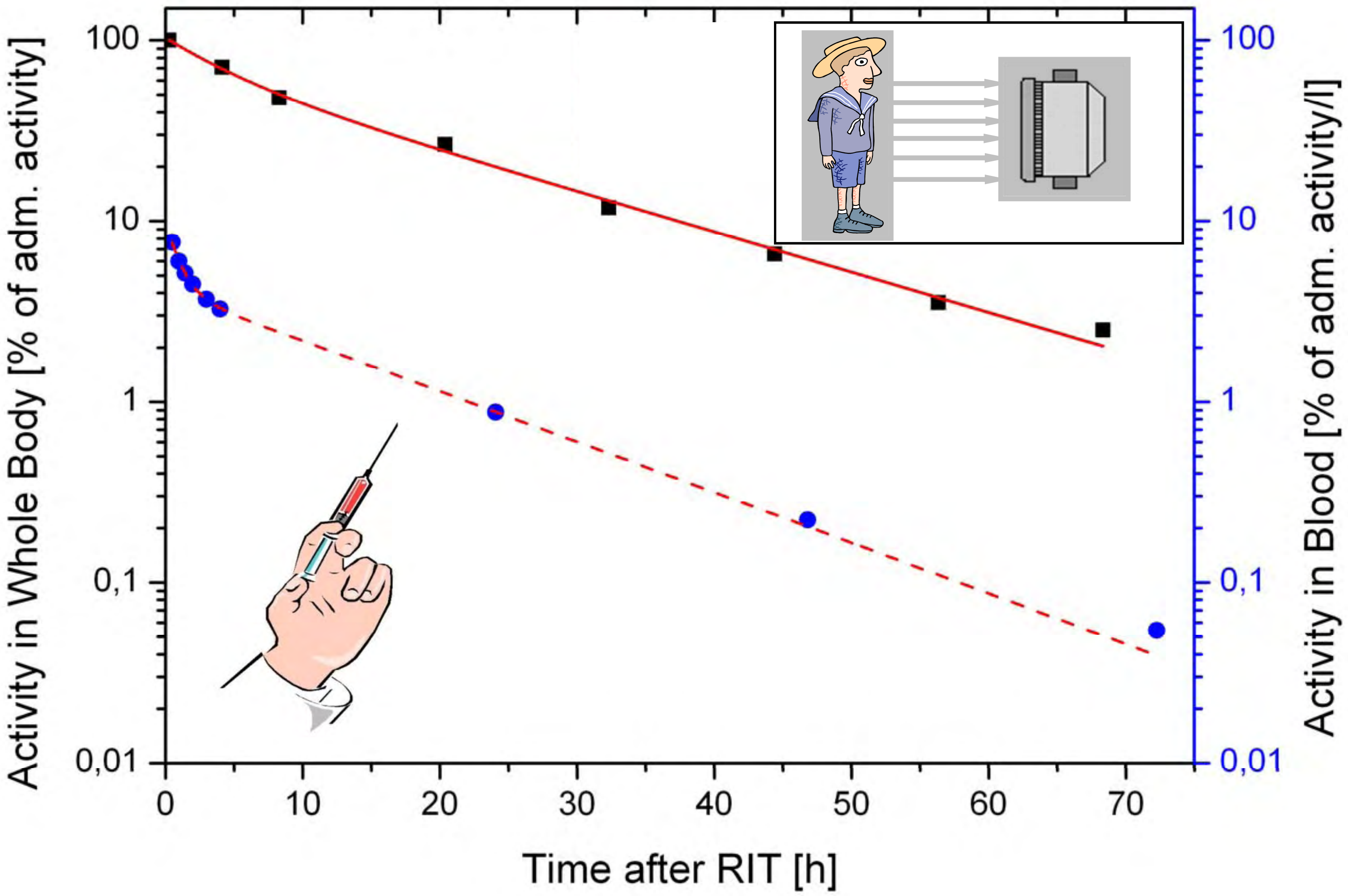
TABLE V

COMPLICATIONS AND RESULTS IN RELATION TO BLOOD TOTAL RADIATION

Blood Total Radiation (rads)	No. of Doses	Serious Radiation Complications*			Objective Good Results*		
		Severe	Fatal	Total (per cent)	Sustained	Temporary	Total (per cent)
0–99	5	0	0	0	1	1	40
100–199	24	1	0	4	7	6	54
200–299	33	5	1	18	7	3	30
300–399	7	1	1	29	1	2	43
400–499	9	0	2	22	2	1	33
Over 500	7	2	0	29	1	2	43
Unknown	37	1	0	3	2	7	24
Total	122	10	4	11	21	22	35

* See text for definition of classification

Example I: Absorbed Dose to the Blood in DTC Patients



Example I: Absorbed Dose to the Blood in DTC Patients

$$\frac{D_{\mathrm{Blut}}}{A_0} = \underbrace{S_{\mathrm{Blut}\leftarrow\mathrm{Blut}} \cdot \tau_{\mathrm{mL\ Blut}}}_{\beta\text{-Contribution of I-131}} + \underbrace{S_{\mathrm{GK}\leftarrow\mathrm{GK}} \cdot \tau_{\mathrm{GK}}}_{\gamma\text{-contribution}}$$

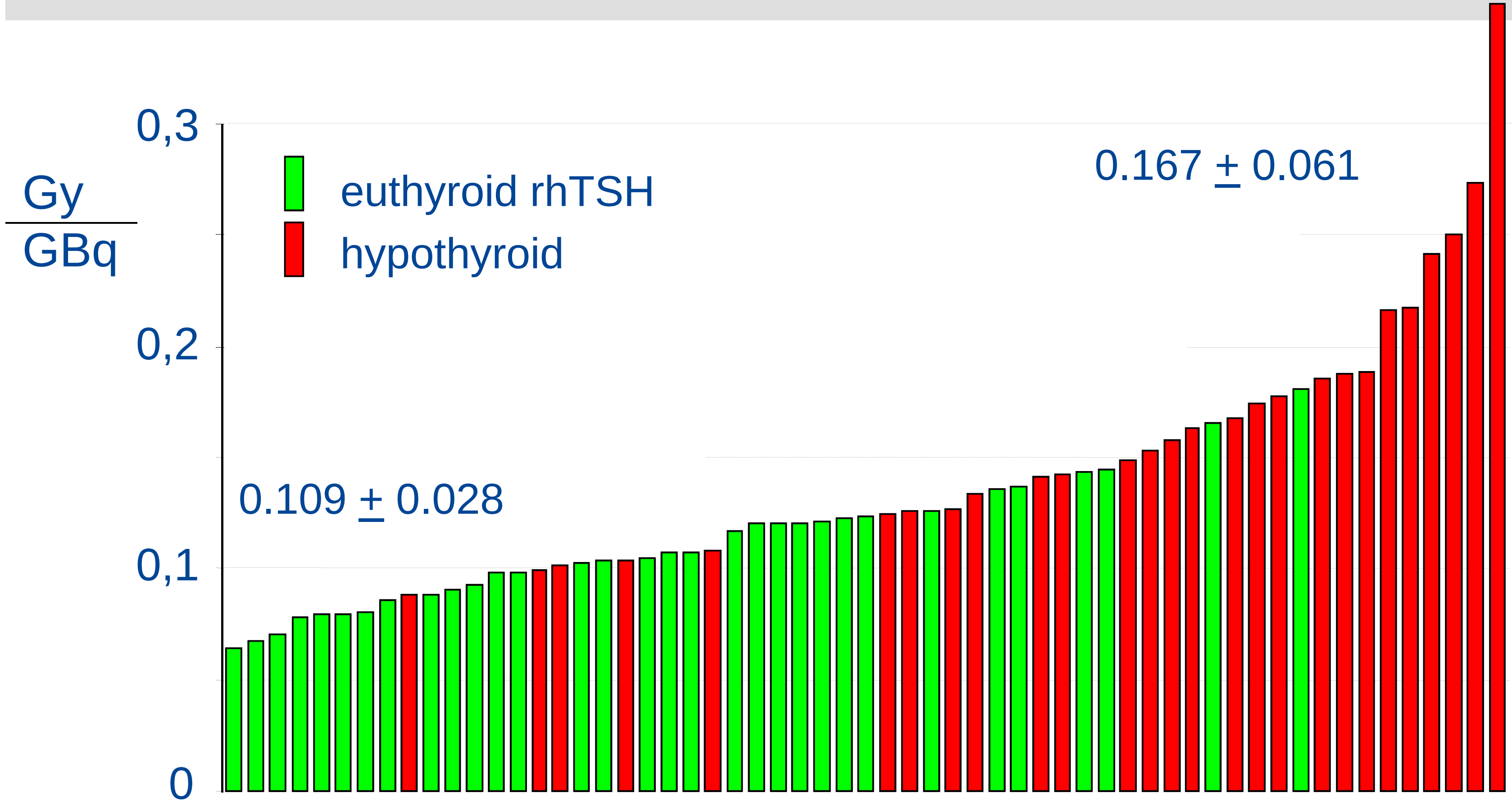
$$\Downarrow$$

$$\frac{D_{\mathrm{blood}}}{A_0}\left[\frac{Gy}{GBq}\right] = 108 \cdot \tau_{\mathrm{ml\ of\ blood}}[h] + \frac{0.0188}{(wt[kg])^{2/3}} \cdot \tau_{\mathrm{TB}}[h]$$

mit	D_{Blood}	Absorbed Dose to the Blood
	A_0	Administered Activity
	$S_{\mathrm{Blut}\leftarrow\mathrm{Blut}}$, $S_{\mathrm{GK}\leftarrow\mathrm{GK}}$	S-Factors
	wt	Body Weight
	$\tau_{\mathrm{ml\ of\ blood}}$	Residence Time per ml of Blood
	τ_{TB}	Whole Body Residence Time

Lassmann M et al. EANM SOP: Blood and Bone Marrow Dosimetry in Differentiated Thyroid Cancer Therapy EJMMI 2008

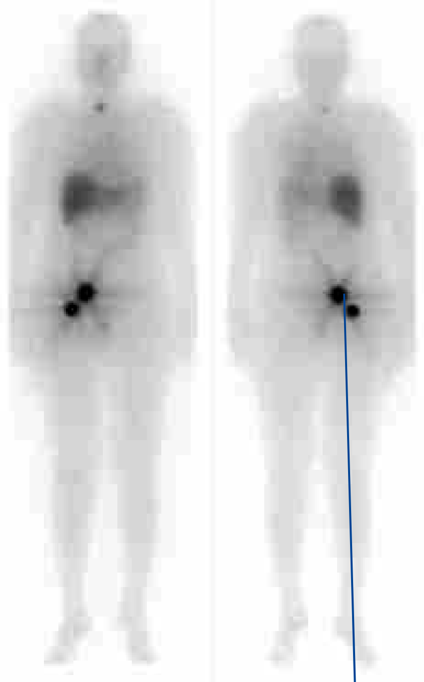
Results: Distribution of Blood Doses after Therapy (66 patients)



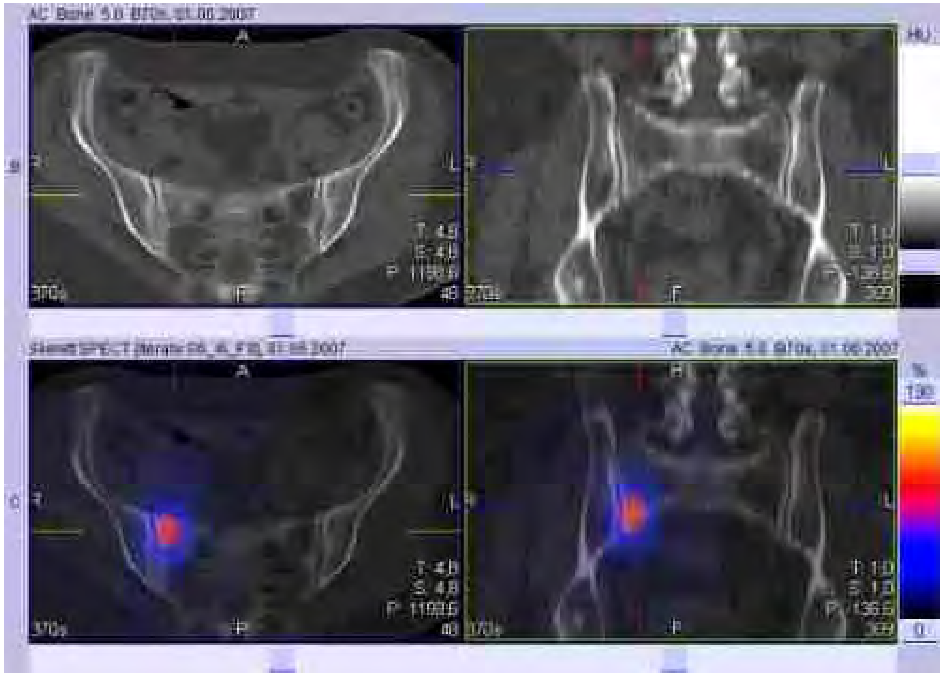
- 66 post-therapeutic (PT) assessments after administration of 3-5 GBq
- Determination of radioiodine kinetics by taking blood samples and measuring whole body activities at least 96h after the administration of I-131

Hänscheid et al. JNM 2006

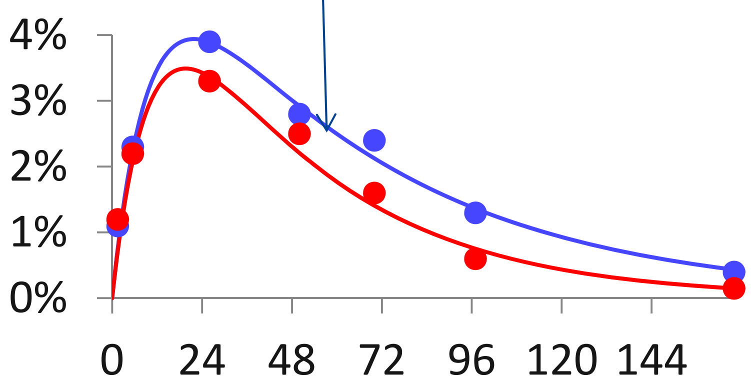
Example II: Absorbed Dose to Metastases in a DTC Patient



Post-therapy scintigram

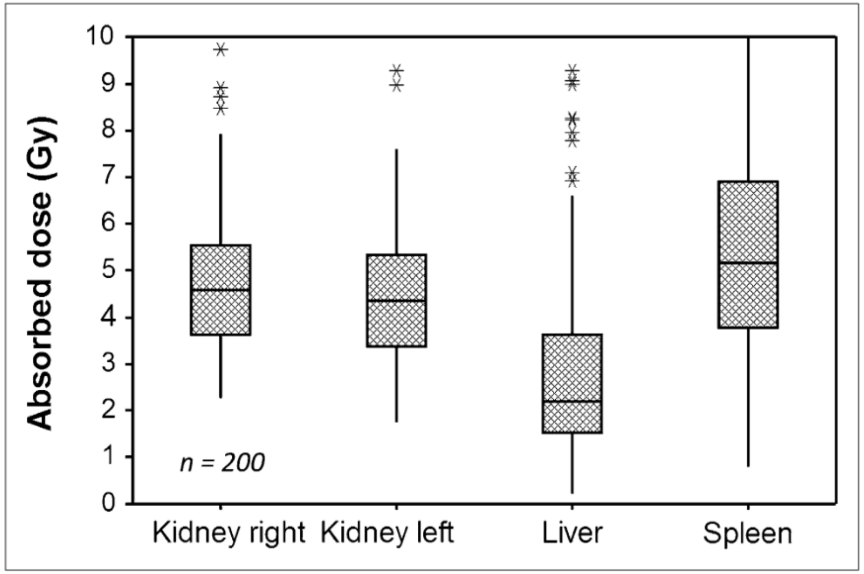


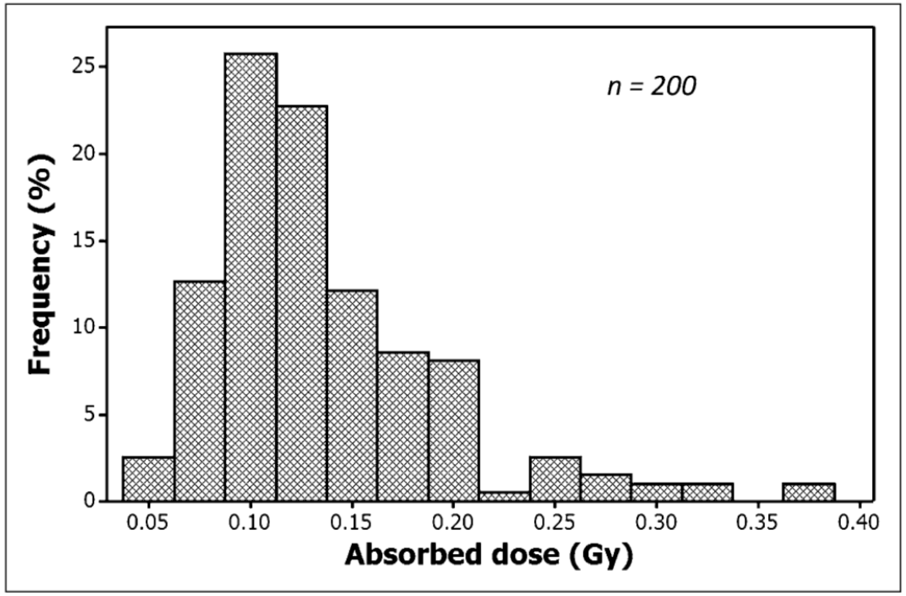
SPECT-CT



Radioiodine kinetics of the osseous metastases

Example III: Dosimetry in Radiopeptide Therapy



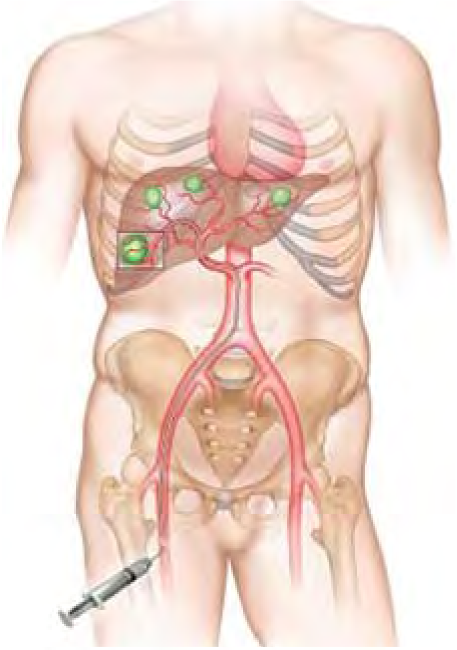


Individualized Dosimetry of Kidney and Bone Marrow in Patients Undergoing ^{177}Lu-DOTA-Octreotate Treatment

J Nucl Med 2013; 54:1–9

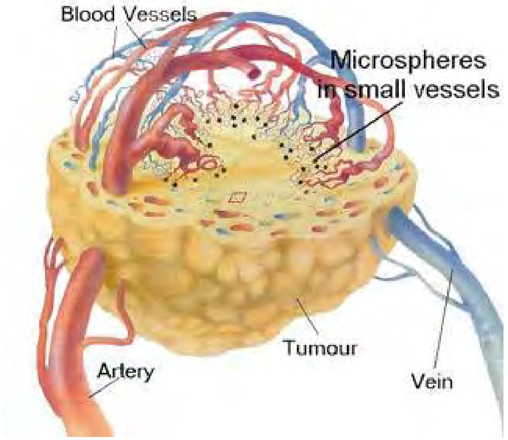
Mattias Sandström[1,2], Ulrike Garske-Román[2,3], Dan Granberg[3], Silvia Johansson[2], Charles Widström[1], Barbro Eriksson[3], Anders Sundin[2,4], Hans Lundqvist[5], and Mark Lubberink[2]

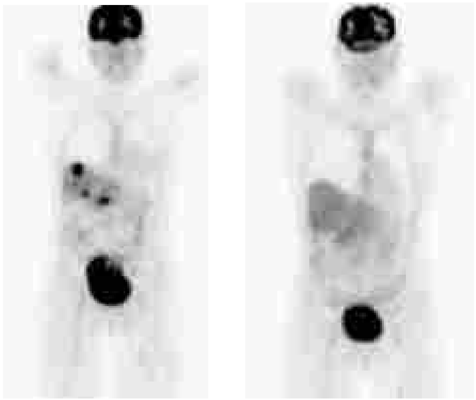
Example IV: Selective Internal Radiotherapy



Transarterial embolization of radioactive labeled microspheres (Y-90)

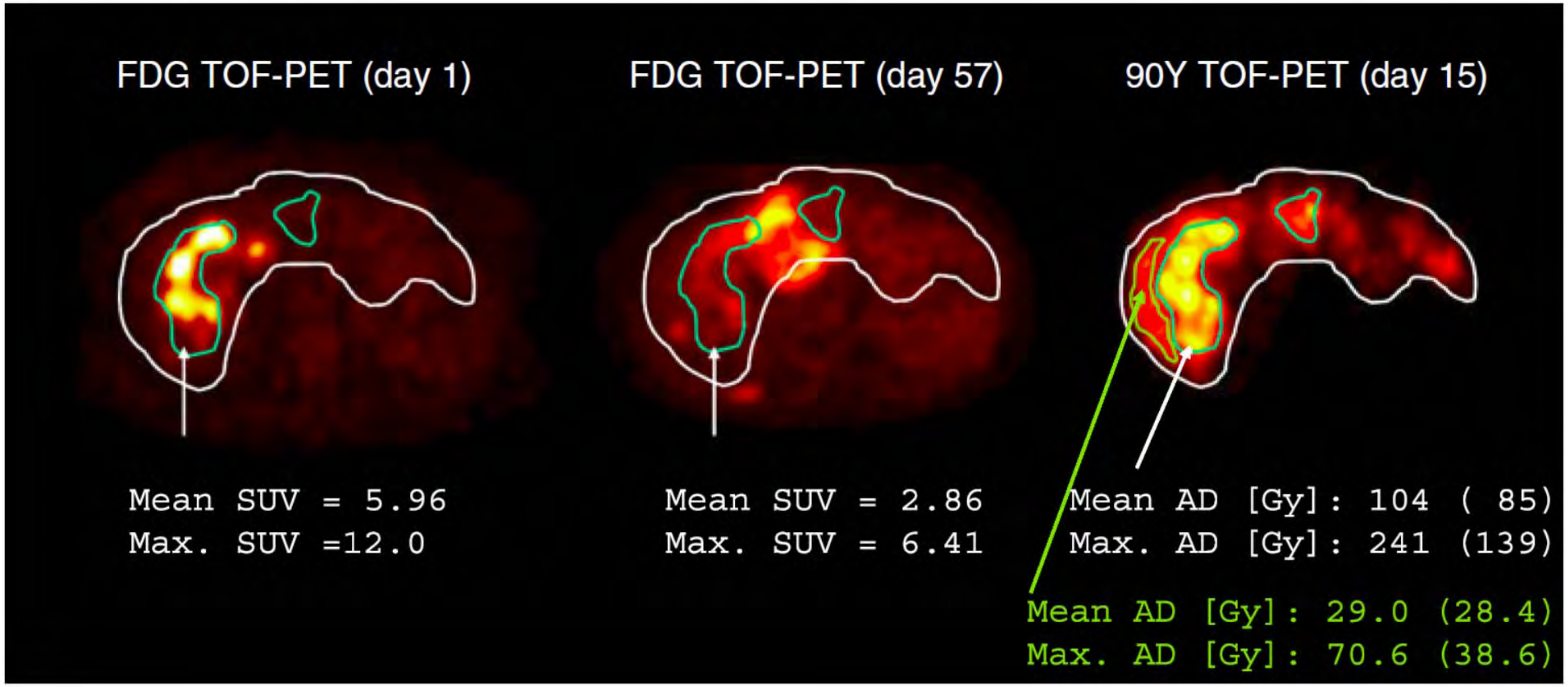
Highly selective tumor uptake by intra-arterial administration of the particles through the a. hepatica





http://nuk.klinikum.uni-muenchen.de/therapie/014_ther_sirt.php
http://www.sec.gov/Archives/edgar/data/873364/000110465903001888/j7431_ex99d1.htm

Example IV: Selective Internal Radiotherapy



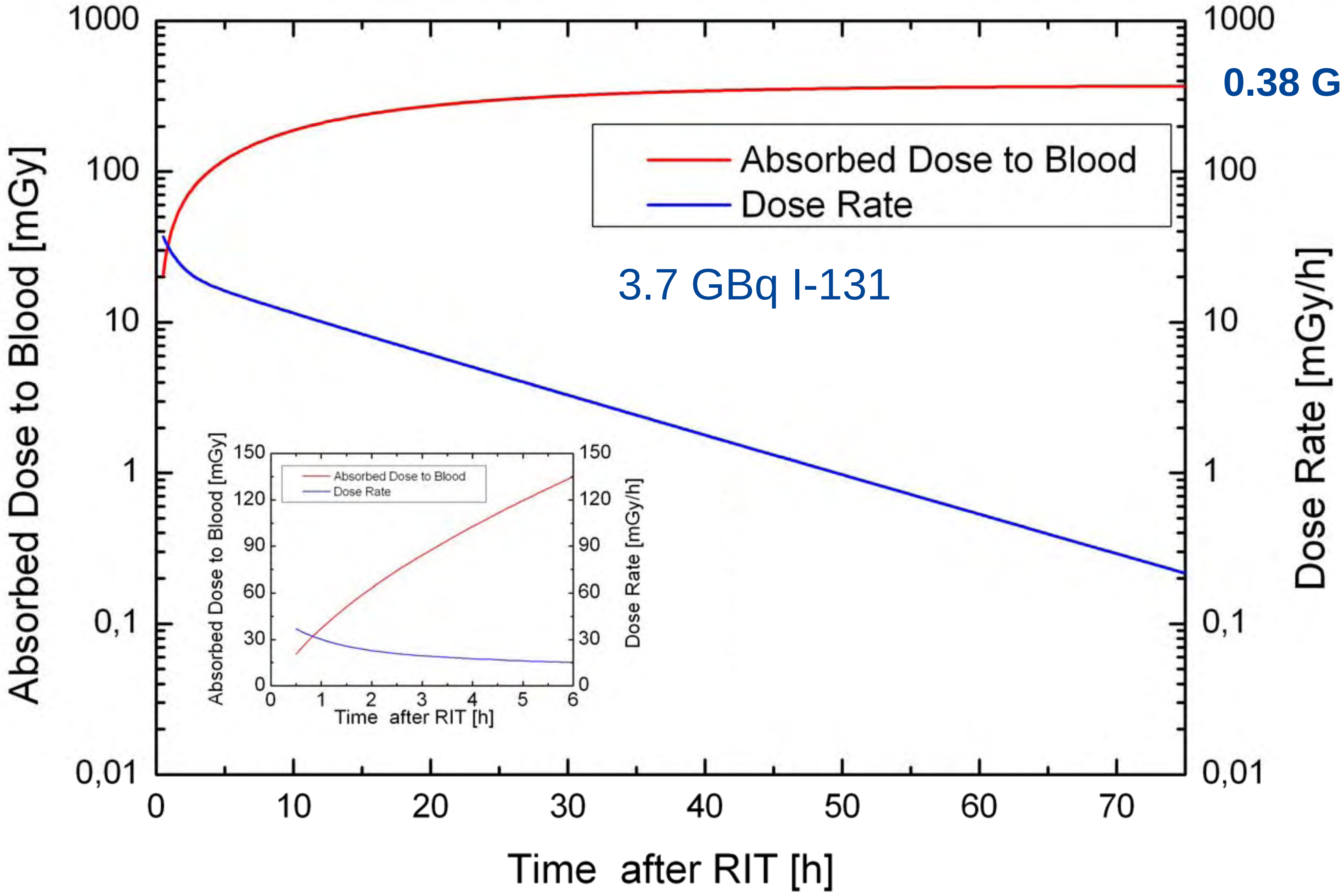

Eur J Nucl Med Mol Imaging (2010) 37:1654–1662
DOI 10.1007/s00259-010-1470-9

ORIGINAL ARTICLE

Feasibility of ^{90}Y TOF PET-based dosimetry in liver metastasis therapy using SIR-Spheres

**Renaud Lhommel · Larry van Elmbt · Pierre Goffette ·
Marc Van den Eynde · François Jamar ·
Stanislas Pauwels · Stephan Walrand**

Absorbed Dose to the Blood in DTC Patients



0.38 Gy

3.7 GBq I-131

Eberlein et al., EANM Congress 2012

Conclusions

- General equation :

$$\overline{D}_k = \sum_h \tilde{A}_h \cdot S_{(k \leftarrow h)}$$

- Dosimetry can accommodate various clinical situations; relies on important hypotheses:
  - Homogeneous activity in each source
  - Calculation of MEAN absorbed dose in the target

- Three Steps to Successful Dosimetry in Nuclear Medicine:
  - Quantitative Imaging
  - Integration of the Time-Activity Curve
  - Determination of the S-Values

- Dosimetry is successful in a many clinical applications