Deutsche Gesellschaft für Nuklearmedizin e.V.

SUMMER SCHOOL 2018

Translational Research in Molecular Imaging and Radionuclid Therapy

August 30 – September 1, 2018

Dosimetry

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What is Dosimetry?

- is the measurement of the **absorbed dose (unit: Gray [Gy])** delivered by ionizing radiation.
  - **External dosimetry** due to irradiation from an external source is based on measurements with a dosimeter.
  - **Internal dosimetry** due to the ingestion or inhalation of radioactive materials relies on a variety of physiological or imaging techniques.

Why Internal Radiation Dosimetry?

Therapy in Nuclear Medicine

- for accurate therapeutic dose prescription
- pre-therapeutically
  - Prediction of the activity needed for achieving the desired effect in the planning target volume or organ
  - Prediction of the maximum tolerable activity for organs at risk (OARs)
- peri-therapeutically
  - Determination of the actual absorbed dose in the target volume or organ and other organs

Why Internal Radiation Dosimetry?

Therapy in Nuclear Medicine

…

Diagnostic Imaging in Nuclear Medicine

- Determination of suited activity to balance potential hazard to patient (diagnostic reference values)

Staff and helping persons

- Determination of absorbed dose according to law (in Germany: Strahlenschutzverordnung (StrlSchV))

Nomenclature, Disambiguation of Terms

- Still not fully accepted definition

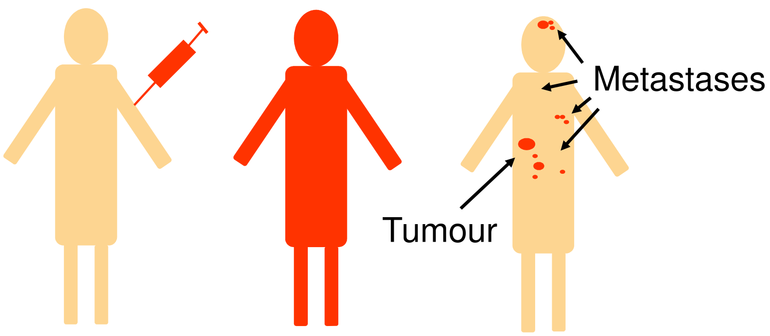
Endoradiotherapy (ERT)
- umbrella term

Targeted Radionuclide Therapy (TRT)
- without individual patient imaging, i.e. no individual dosimetry
- like chemotherapy, population based

Molecular Radiotherapy (MRT)
- with individual patient imaging, i.e. individual dosimetry
- like in radiation therapy, individualized

Overview

1. Endoradiotherapy (ERT)



Courtesy of Prof. Dr. Flavio Forrer, Universitätsspital Basel, Switzerland

1. Endoradiotherapy (ERT)

- Injection of **radiolabelled substances**
- Radionuclides with **short range** radiation
  – α-, β-, Auger emitter
- Selective irradiation due to **accumulation in target volume**
  – local application (e.g., radiosynoviortesis)
  – use of a specific transporter or receptor system for the organ specific accumulation
    - e.g. transporter = antibody,
      ⇒ Radio*immuno*therapy (RIT)

Endoradiotherapy

"Systemic Radiotherapy"

analogous to chemotherapy:

= amount of drug = radioactivity (MBq) per
body weight (MBq/kg) or
body surface (MBq/m^2)

analogous to radiotherapy:

= absorbed dose (Gy)

Aim: Maximizing the therapeutic index

=> Dose (Gy) in target organ / organs at risk

1.a Radionuclides used in ERT

	Energy MeV	mean range (water) µm	CDM*
• β^--particles	~ 1	~ 3000	300
• α-particles	~ 5	~ 50	5
• Auger-e^-	~ 0.001	~ 0.01	0.001

*cell diameter

Radionuclides (Examples)

Radio-nuclide	$t_{1/2}$ *(d)*	*Max / MW ß-Energy (keV)*	*Max / 90% Range (mm)*	*γ-Energy (keV)*
^{131}Iodine	*8.0*	*606*	*2 / 1.5*	*364 (82%)*
^{177}Lutetium	*6.7*	*500 / 130*	*2 / 1.5*	*113 (6.6%) 208 (11%)*
^{90}Yttrium	*2.7*	*2280 / 935*	*12 / 5.3*	*-*
^{111}Indium	*2.8*	*14.7 (Auger)*	*0.04 / 0.008*	*172 (90%) 247 (94%)*

1.b Radiopharmaceuticals/Endoradiotherapies

The use of different radiopharmaceuticals constitutes different ERTs:

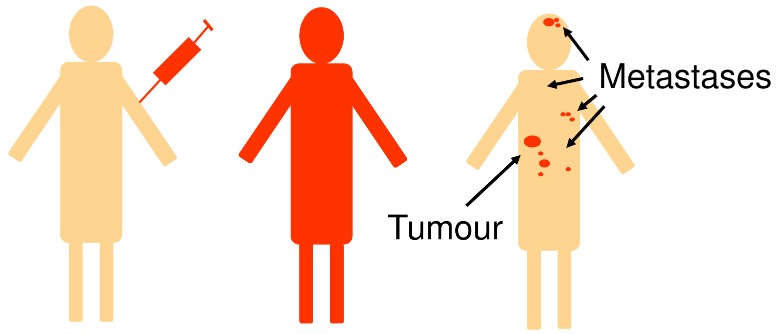
- Radioiodine therapy => ^{131}I
- **Radioimmunotherapy (RIT) => antibodies**
- **Peptide Rezeptor RadioTherapy (PRRT) => peptides**
- Palliation of bone metastases => ^{89}Sr, ^{153}Sm, …
- Radiosynoviortesis (RSO) => ^{90}Y-, ^{169}Er-, ^{186}Re-colloid
- …

Note:

Biodistribution/Biokinetics depends mostly on the compound and only a little bit on the attached radionuclide.

1. Endoradiotherapy (ERT)

Which activity to inject?



Courtesy of Prof. Dr. Flavio Forrer, Universitätsspital Basel, Switzerland

2.a Activity Determination: „Dose“ Escalation Trial

Analogous to **Chemotherapy**

- Amount of drug (activity) per mass of body weight or surface area:
  => MBq, MBq/kg or MBq/m^2

Activity escalation trial

- Treat small groups of patients (3-6 patients)
- Increase activity for each group step by step
- If toxicities become severe => activity is lowered by one step
- This activity is defined as the “optimal” activity

Inter-patient variability neglected (e.g. pharmacokinetics, sensitivity, …)

Thus: under- or over-treatment of patients

2.b Activity Determination: Dosimetry-Based

Objective:

- achieve a prescribed **individual** tumour **absorbed dose**
- while minimizing normal tissues toxicities

⇒ as in Radiation Therapy!

Individual Dosimetry

Individual measurement of (radio)activity

- - spatial and
- - temporal distribution

and calculation (using electron density distribution) of

- absorbed dose per injected activity in tissues (Gy/GBq).

Procedure:

- administration of a radiopharmaceutical (activity and amount)
- measurement of biokinetics (⇒ number of decays in the considered organ)
- calculation of absorbed doses

Quantification

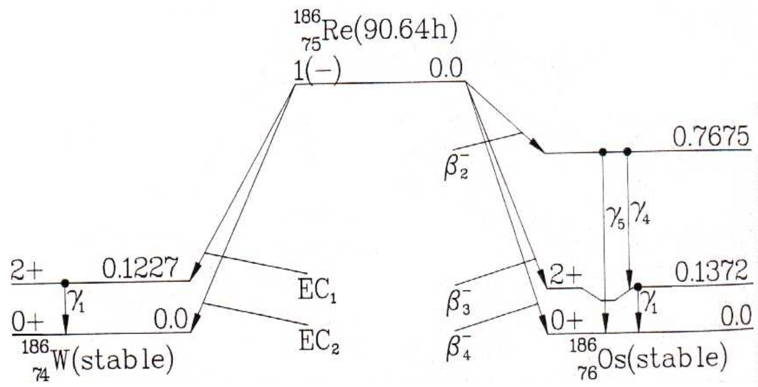
(Radiation) **absorbed dose** in tissues (Gy = J/kg)

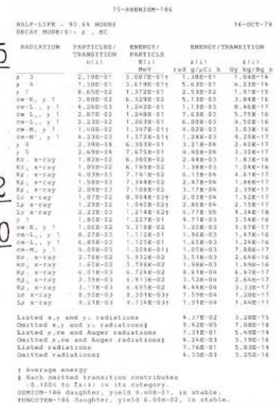
3 Components must be considered:

- (radiation) physical component
  - emitted energy per decay,
  - absorbed energy (spatial distribution)
- geometrical component
  - mass and geometry of organs
  - relative positions between irradiating and irradiated organ
- biological component
  - biokinetics
  - biological effectiveness (e.g. dose rate dependence)

Physical Component

- administered activity (Bq)
- mean energy per mode of decay and its probability





MIRD radionuclide data and decay schemes
Weber DA, Eckerman KF, Dillman LT and Ryman JC, The Society of Nuclear Medicine, N.Y. 1989

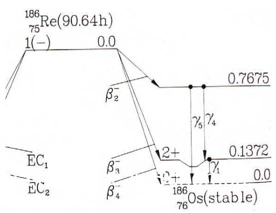
75-RHENIUM-186

HALF-LIFE = 90.64 HOURS 16-OCT-78
DECAY MODE(S): β⁻, EC

RADIATION	PARTICLES/ TRANSITION n(i)	ENERGY/ PARTICLE E(i) MeV	ENERGY/TRANSITION Δ(i) rad g/µCi h	Δ(i) Gy kg/Bq s
β⁻ 3	2.10E-01	3.087E-01†	1.38E-01	1.04E-14
β⁻ 4	7.30E-01	3.619E-01†	5.63E-01	4.23E-14
γ 1	8.65E-02	1.372E-01	2.53E-02	1.91E-15
ce-K, γ 1	3.80E-02	6.329E-02	5.13E-03	3.84E-16
ce-L₁, γ 1	4.26E-03	1.242E-01	1.13E-03	8.46E-17
ce-L₂, γ 1	2.87E-02	1.248E-01	7.63E-03	5.75E-16
ce-L..., γ 1	2.23E-02	1.263E-01	6.00E-03	4.50E-16

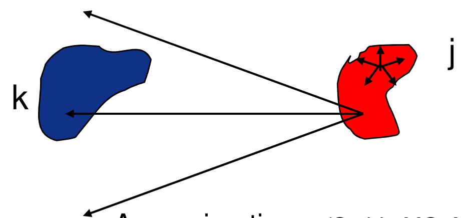
Listed x,γ and γ± radiations	4.37E-02	3.28E-15
Omitted x,γ and γ± radiations‡	9.42E-05	7.08E-18
Listed β,ce and Auger radiations	7.31E-01	5.49E-14
Omitted β,ce and Auger radiations‡	4.24E-03	3.19E-16
Listed radiations	7.76E-01	5.83E-14
Omitted radiations‡	4.33E-03	3.25E-16

† Average energy
‡ Each omitted transition contributes
<0.100% to ΣΔ(i) in its category.
OSMIUM-186 daughter, yield 9.40E-01, is stable.
TUNGSTEN-186 daughter, yield 6.00E-02, is stable.



Geometrical Component

ϕ_{ijk} = fraction of emitted energy of mode of radioactive decay *i* in source organ *j*, which is absorbed in organ *k*



in priniciple one must take into account the (inhomogeneous) spatial distribution

=> not practical

Approximations: (Stabin MG. MIRDOSE: Personal Computer Software for Internal Dose Assessment in Nuclear Medicine. J Nucl Med 1996; 37: 538-546)

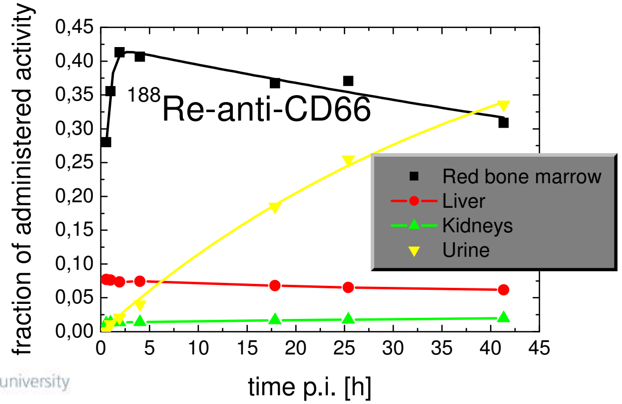
1. Activity is distributed homogeneously within the organ
2. Standard phantoms: (fixed organ masses and organ geometries, available for a variety of ages, pregnant females)
3. absorbed doses

   β radiation: "range zero" (exposition only within the source organ)

Biological Component

Time-integrated activity coefficient (outdated: residence time) τ_j
= Number of decays in organ *j* / adminstered activity

Determination: measurement of the time activity curves in respective tissues followed by integration over time



3. Medical Internal Radiation Dose Committee (MIRD)

- A committee of the Society of Nuclear Medicine (SNM, USA), founded 1968
- Members: Physicists and physicians
- Publishes usually in the Journal of Nuclear Medicine (JNM)
  - 23 MIRD pamphlets
  - 20 dose estimation reports
  - 3 books
- No own hompage, but uses www.snm.org or the JNM

MIRD Reference Books

First: Details of the MIRD scheme

MIRD primer for absorbed dose calculations
Loevinger R, Budinger TF and Watson EE,
The society of nuclear medicine, N.Y. 1988, rev. 1991

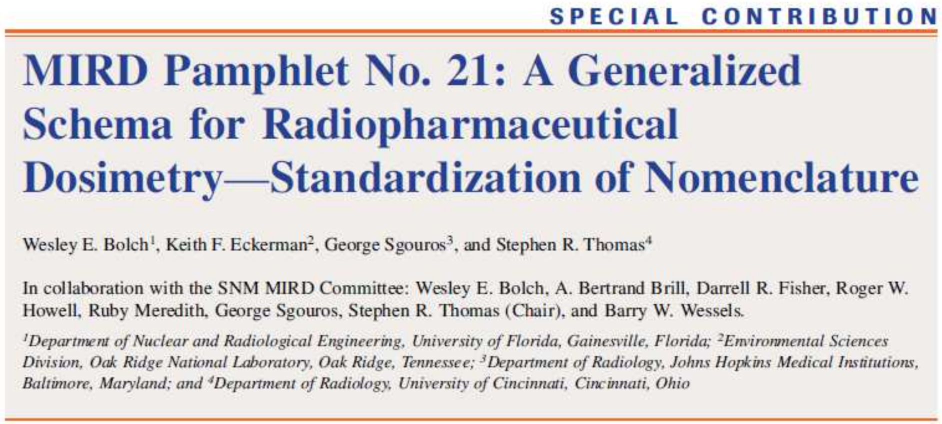
Second: Physical data

MIRD radionuclide data and decay schemes
Weber DA, Eckerman KF, Dillman LT and Ryman JC,
The society of nuclear medicine, N.Y. 1989

Third: Data for calculations on the cell level

MIRD Cellular S Values
Goddu SM, Howell RW, Bouchet LG, Bolch WE and Rao DV
The society of nuclear medicine, N.Y. 1998

MIRD vs. ICRP: J Nucl Med 2009; 50:477–484



SPECIAL CONTRIBUTION

MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature

Wesley E. Bolch[1], Keith F. Eckerman[2], George Sgouros[3], and Stephen R. Thomas[4]

In collaboration with the SNM MIRD Committee: Wesley E. Bolch, A. Bertrand Brill, Darrell R. Fisher, Roger W. Howell, Ruby Meredith, George Sgouros, Stephen R. Thomas (Chair), and Barry W. Wessels.

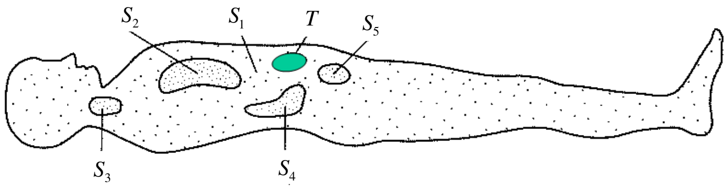
[1]Department of Nuclear and Radiological Engineering, University of Florida, Gainesville, Florida; [2]Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee; [3]Department of Radiology, Johns Hopkins Medical Institutions, Baltimore, Maryland; and [4]Department of Radiology, University of Cincinnati, Cincinnati, Ohio

ICRP = International Commission on Radiological Protection

4. MIRD Dosimetry in Endoradiotherapy (ERT)

$$D(r_T) = A_0 \cdot \sum_{r_S} \tilde{a}(r_S) \cdot S(r_T \leftarrow r_S)$$

Absorbed dose → $D(r_T)$; Admin. activity → A_0; S value → $S(r_T \leftarrow r_S)$; Target organ → r_T; Time-integrated activity coefficient → $\tilde{a}(r_S)$; Source organ → r_S



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$$\tilde{a}(r_S) = \frac{1}{A_0} \int_0^\infty A(r_S, t)\, dt$$

Time-activity-curve in source region → $A(r_S, t)$

Number of decays → $\int_0^\infty A(r_S, t)\, dt$

Medical Internal Radiation Dose (MIRD) S values

$$S(r_T \leftarrow r_S) = \sum_i n_i\, E_i\, \phi_i(r_T \leftarrow r_S) / m_T$$

with

$i =$ Denominates different decay modes

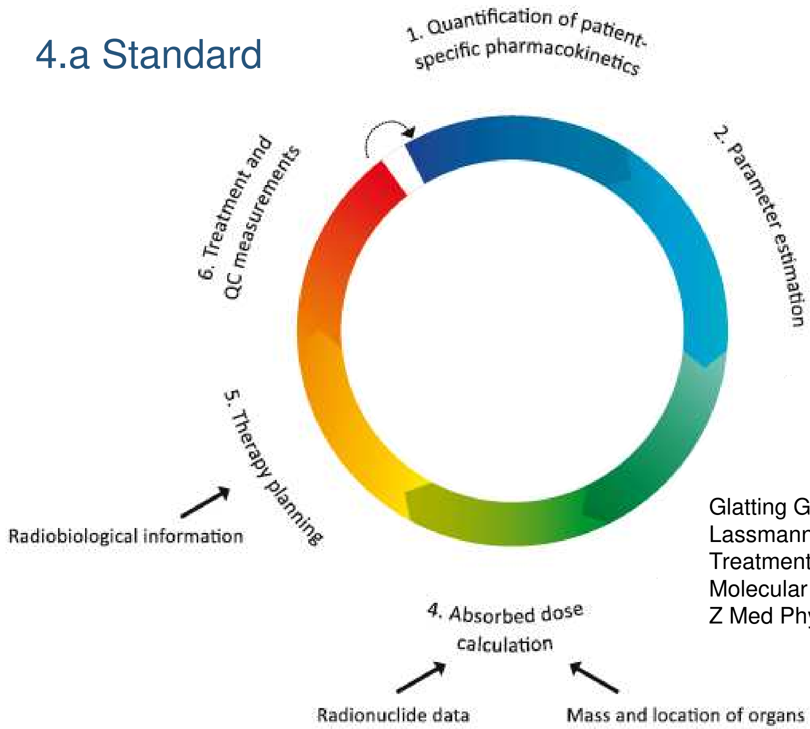
$n_i =$ Transition probability for mode i

$E_i =$ Energy of decay of mode i

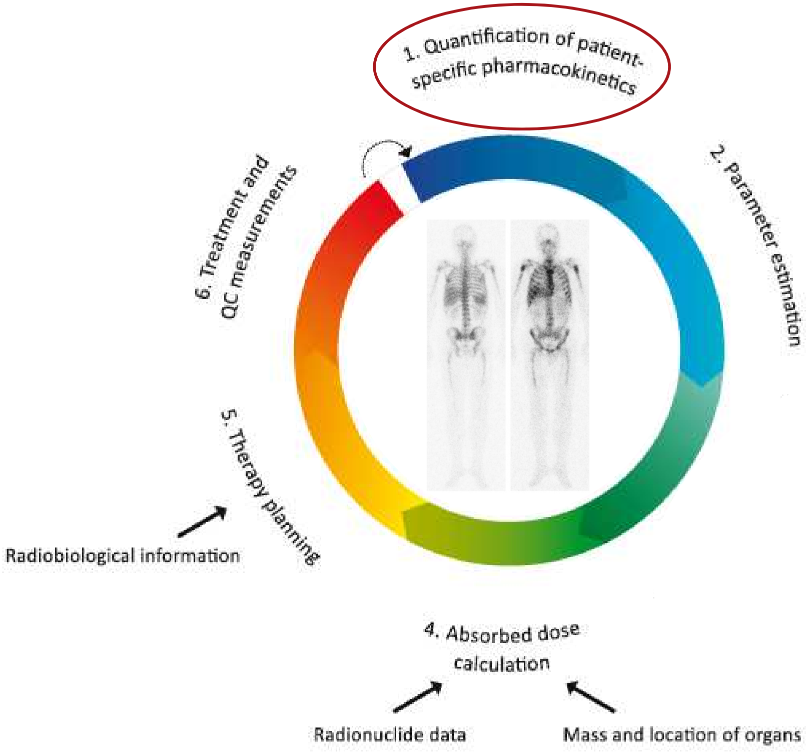
$\phi_i(r_T \leftarrow r_S) =$ Absorbed fraction in target organ T for a decay of mode i in the source organ S

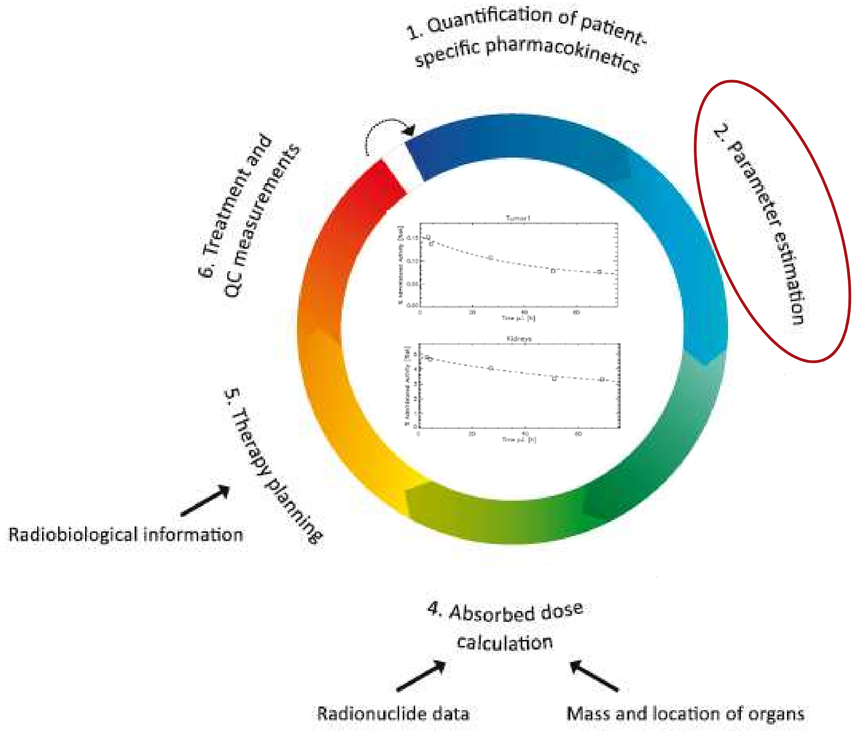
m_T Mass of the target organ

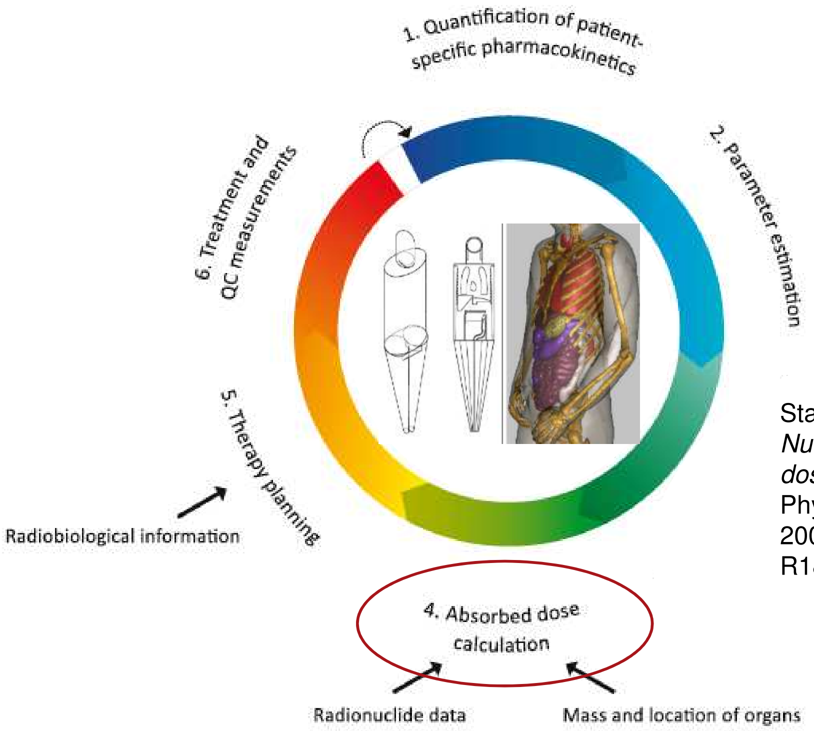
4.a Standard



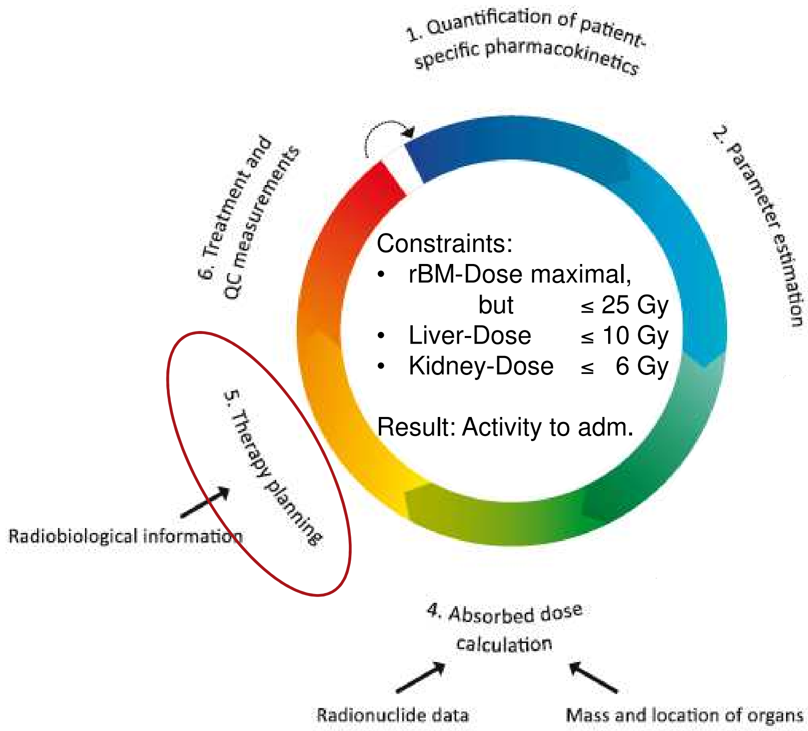
Glatting G, Bardiès M, Lassmann M. Treatment Planning in Molecular Radiotherapy. Z Med Phys 2013; 23: 262-9.

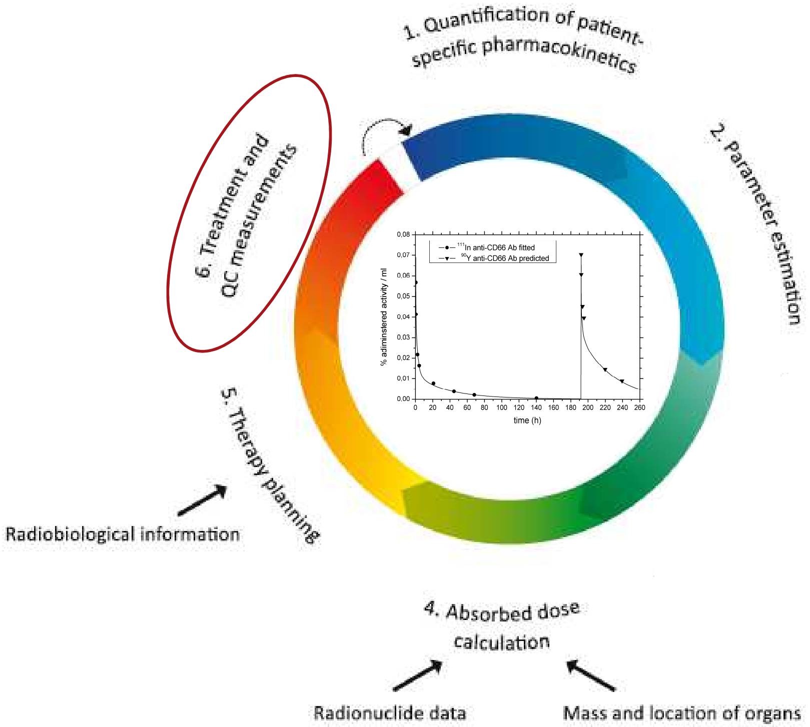




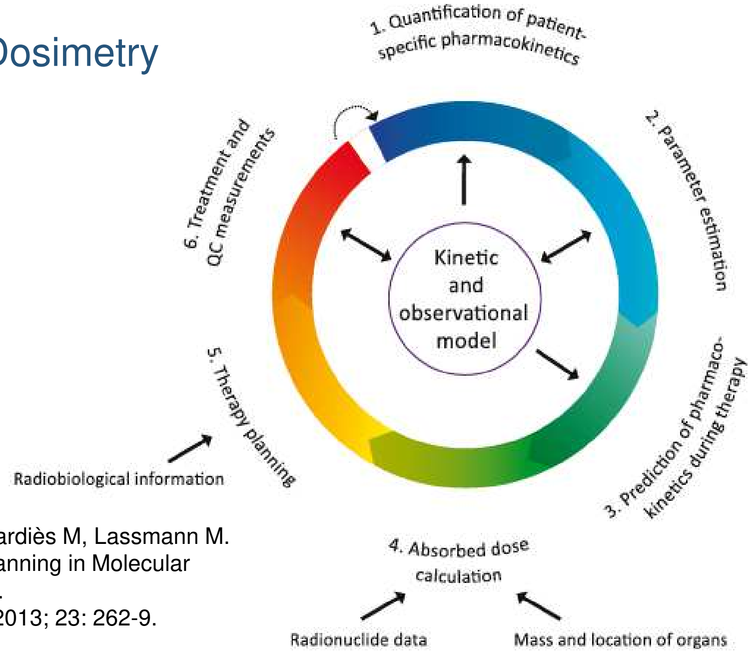


Stabin, M., *Nuclear medicine dosimetry.* Phys Med Biol 2006; **51**(13): R187-202.





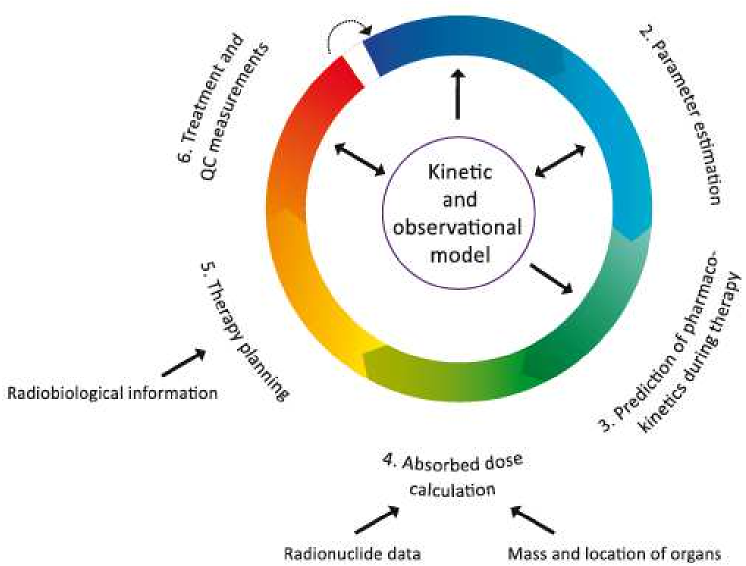
4. Dosimetry



Glatting G, Bardiès M, Lassmann M. Treatment Planning in Molecular Radiotherapy.
Z Med Phys 2013; 23: 262-9.

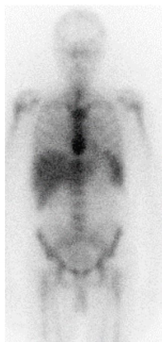
4.b Advanced

$$D(r_T) = A_0 \cdot \sum_{r_S} \tilde{a}(r_S) \cdot S(r_T \leftarrow r_S)$$



… in the past … … now and in the future?

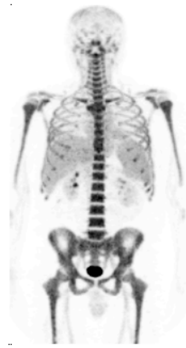
conventional scintigraphy
[^{188}Re]anti-CD66, AML



Advantages:
- estimation of organ doses possible

Disadvantages:
- planar data
- region drawing

PET/CT
[^{18}F]anti-CD66, AML



Advantages:
- sensitivity (factor 100)
- tomographic data

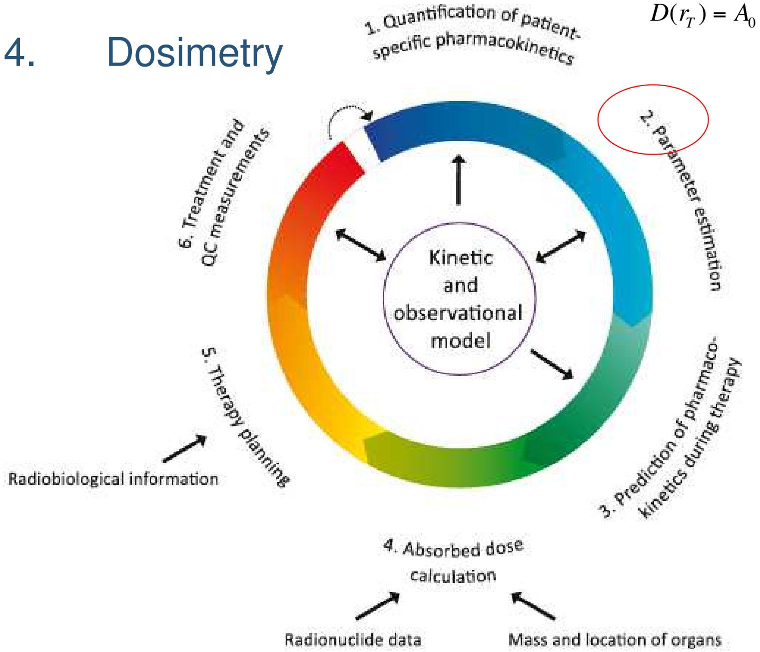
Disadvantages:
- short half-lifes of nuclides (^{18}F, ^{68}Ga) $\Rightarrow$ modelling

or

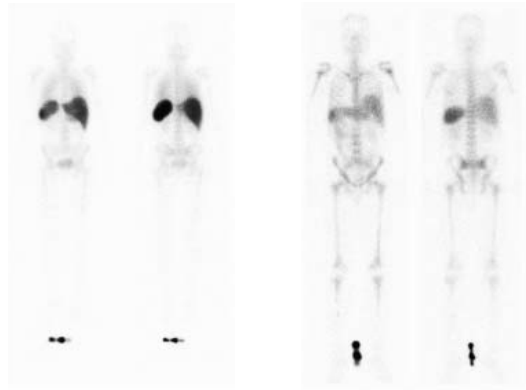
- non-pure β^+ emitter (^{86}Y)

4. Dosimetry

$$D(r_T) = A_0 \cdot \sum_{r_S} \tilde{a}(r_S) \cdot S(r_T \leftarrow r_S)$$



Modulation of Biodistribution: Example



without with

0,5 mg/kg unlabelled mab

Glatting et al. J Nucl Med 2006;47:1335-41

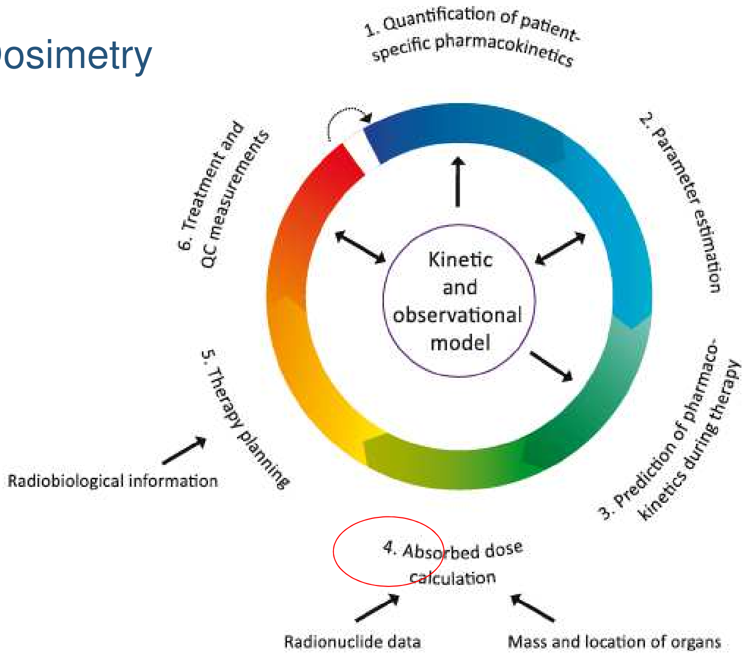
^{111}In-labelled anti-CD45 monoclonal antibodies

used for

Intensification of conditioning before stem cell transplantation (when labelled with ^{90}Y)

*Therapy may become better **and** cheaper!*

4. Dosimetry



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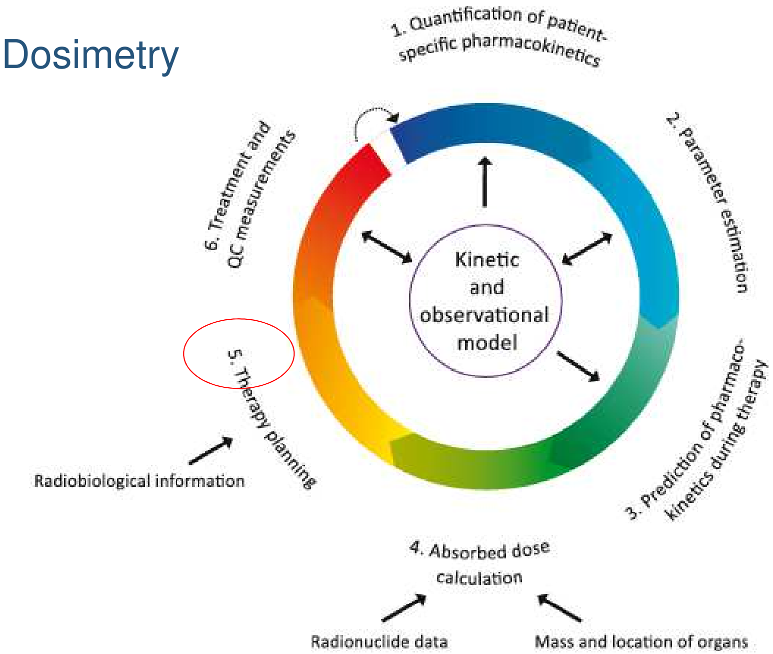
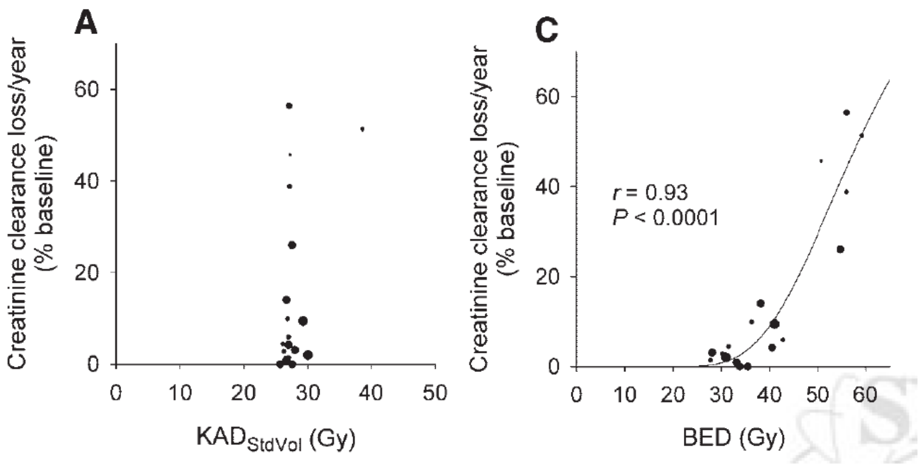


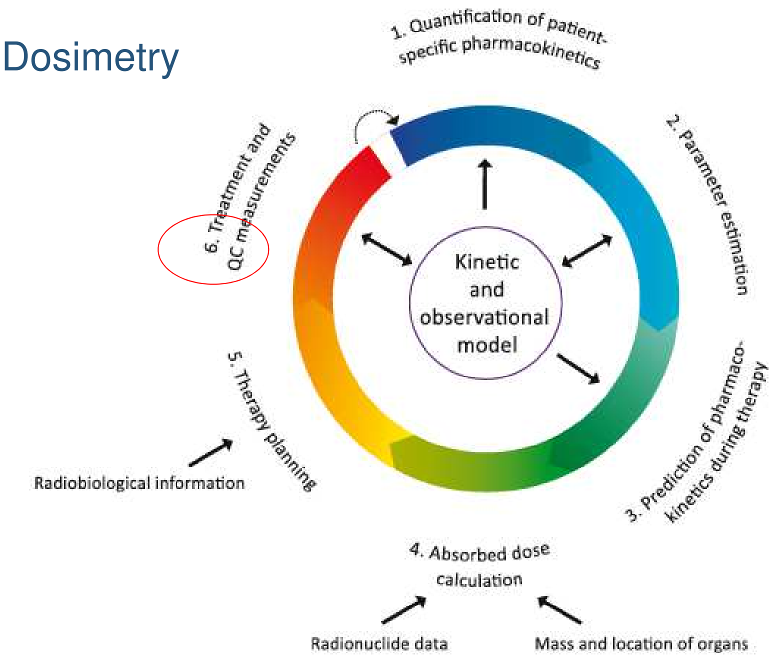
Biologically Effective Dose (BED): Kidneys

Dose-response relationship



Barone et al. J Nucl Med 2005

4. Dosimetry



5. Conclusion

Endoradiotherapy is very interdisciplinary:

- Physicians, biologists, (radio)chemists, physicists, engineers, MTRA, …

There is still a lot to do for individualization of therapy!

Individualization allows a considerably improved therapy, e.g. through adjustment of administered activity <u>and</u> antibody/peptide dose (and time schedule).

6. References

Adelstein SJ, Green AJ, Howell RW, Humm JL, Leichner PK, O'donoghue JA, Strand SE, Wessels BW. Absorbed-dose specification in nuclear medicine. Journal of the ICRU 2002; 2: 1-110

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: 477-84

Glatting G, Bardiès M, Lassmann M. Treatment Planning in Molecular Radiotherapy. Z Med Phys 2013; 23: 262-9.

Hindorf C, Glatting G, Chiesa C, Lindén O, Flux G. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. Eur J Nucl Med Mol Imaging 2010; 37: 1238-50

Lassmann M, Chiesa C, Flux G, Bardiès M. EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting. Eur J Nucl Med Mol Imaging 2011; 38: 192-200

Stabin MG. Uncertainties in Internal Dose Calculations for Radiopharmaceuticals. J Nucl Med 2008; 49: 853-60.

http://www.doseinfo-radar.com/