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Developments in patient dosimetry for unsealed sources

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Overview

1. Targeted Radionuclide Therapy (TRT)
2. Activity Determination
   a. Dose Escalation Trial
   b. Dosimetry-Based
3. Dosimetry in TRT
   a. Standard
   b. Advances
   c. Challenges/Opportunities
4. Conclusion

1. Targeted Radionuclide Therapy (TRT)

Objective of TRT:

- maximize tumour cell sterilization while avoiding or minimizing normal tissue toxicities

Procedure:

- 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
    - transporter = antibody, $\Rightarrow$ Radio**immuno**therapy (RIT)
    - transporter = peptide, $\Rightarrow$ Peptide Receptor Radionuclide Therapy (PRRT)

2. 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

Dose escalation trial

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

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

Thus: under- or over-treatment of patients

2. Activity Determination: Dosimetry-Based

Objective:

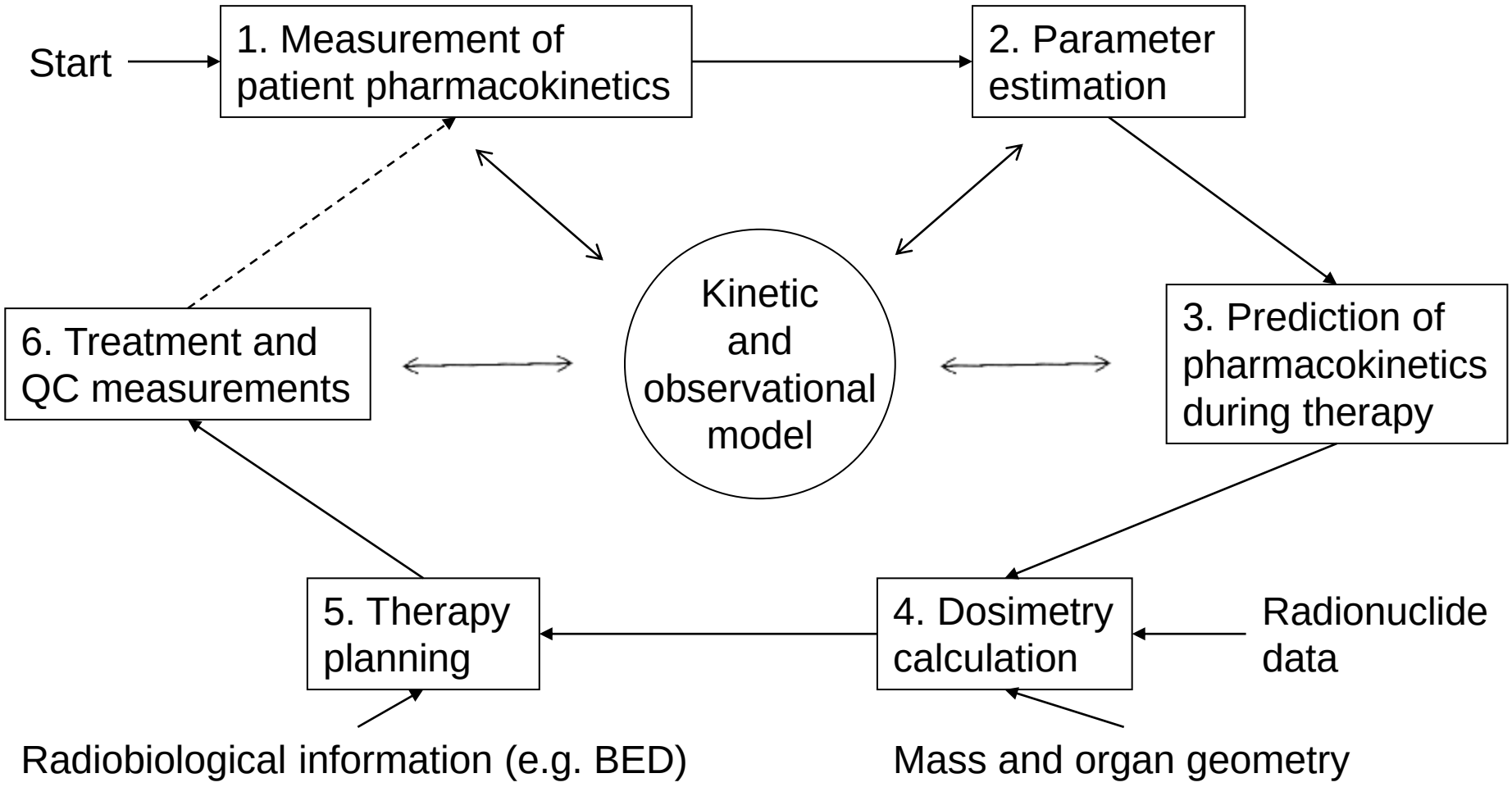
- maximize **individual** tumour **absorbed dose** while avoiding or minimizing normal tissue toxicities

$\Rightarrow$ as in Radiation Therapy!

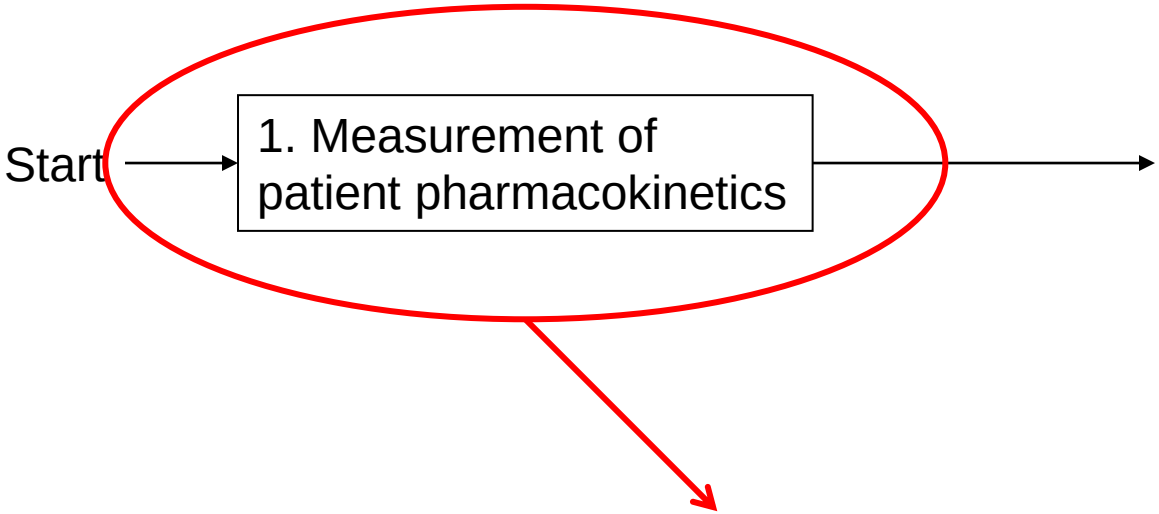
Consequence:

- corresponding challenges apply! (session 2)

3. Dosimetry for TRT: Flowchart



3. Dosimetry for TRT: Flowchart



Quantitative imaging!

3.1 Quantitative Imaging

Standard

- Planar gamma camera imaging
- Manual region drawing

Advances

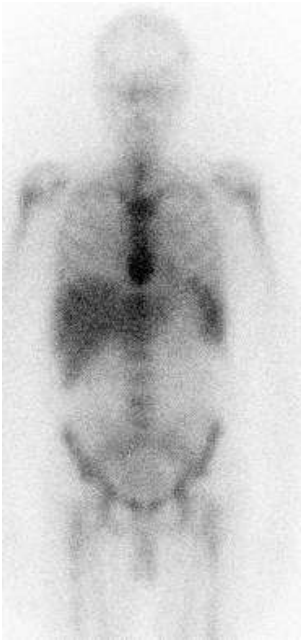
- Tomographic imaging (3D => SPECT/CT, PET/CT, PET/MR)

Challenges/Opportunities

- Implementing corrections for quantification (also: Bremsstrahlung imaging)
- Measurement on small scales (needed for microdosimetry)
- Equipment needed

… in the past …

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



Advantages:

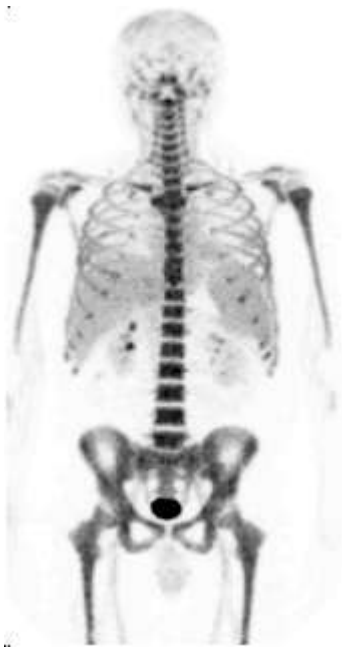
-estimation of organ doses possible

Disadvantage:

-planar data

… in future?

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



Advantages:

-sensitivity (factor 100)

-tomographic data

Disadvantages:

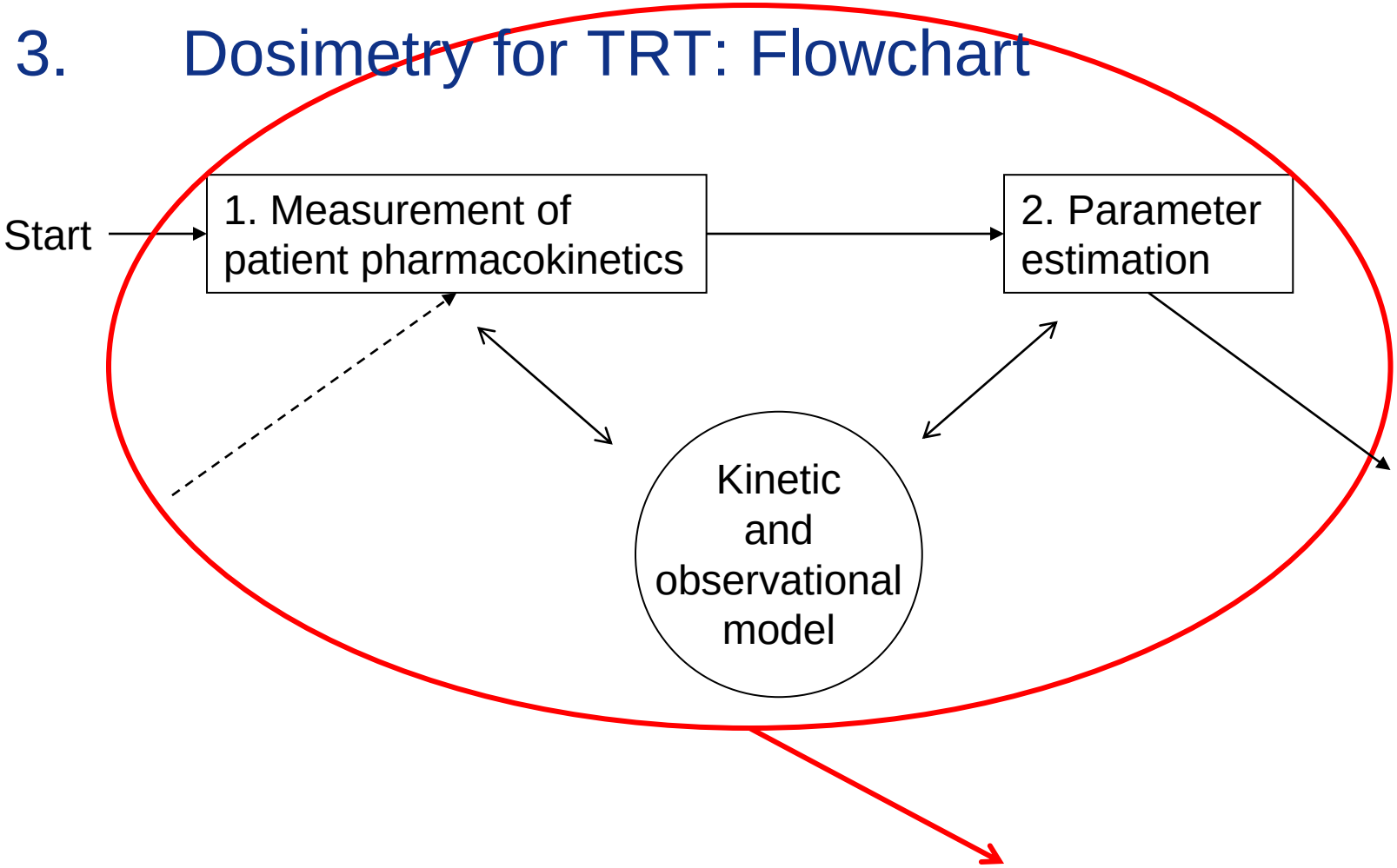
-short half-lifes of nuclides (^{18}F, ^{68}Ga) $\Rightarrow$ modelling

or

-non-pure β^+ emitter (^{86}Y)

Courtesy Prof. S.N. Reske, Nuclear Medicine Clinic, Ulm University, Germany

3. Dosimetry for TRT: Flowchart



- Kinetic Model!
- Temporal Sampling!

3.2a Kinetic Model

Standard

- Fitting kinetic data by sums of exponentials, fit function selection by experience

Advances

- Fitting data by physiologically based pharmacokinetic (PBPK) models, best model selected using an objective criterion (e.g. Akaike information criterion)
- Uncertainty estimation

Challenges/Opportunities

- Education needed and/or (?) sophisticated software
- More accurate estimation of dose or less patient involvement

Physiologically Based Pharmacokinetic (PBPK) Model

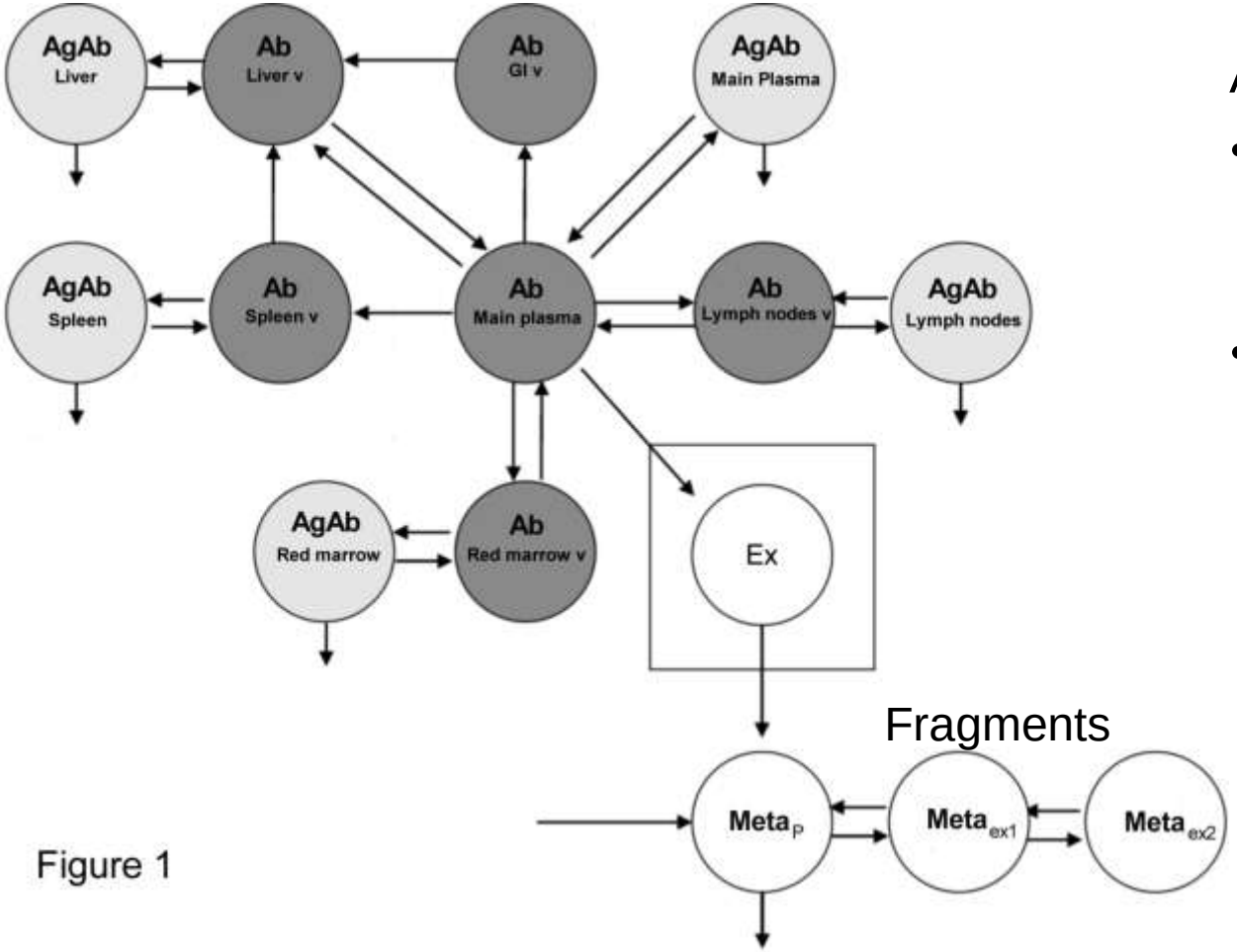


Figure 1

Advantages:

- More accurate determination of parameters
- Parameters represent a physiologic quantity. Thus, predictions of biokinetics for changed conditions can be generated / simulated.

P. Kletting et al. J Nucl Med 2009;50:296-302

3.2b Temporal Sampling Schedule

Standard

- Data sampling schedule using rule of thumb, e.g. 3 measurements for one exponential at „arbitrary“ times

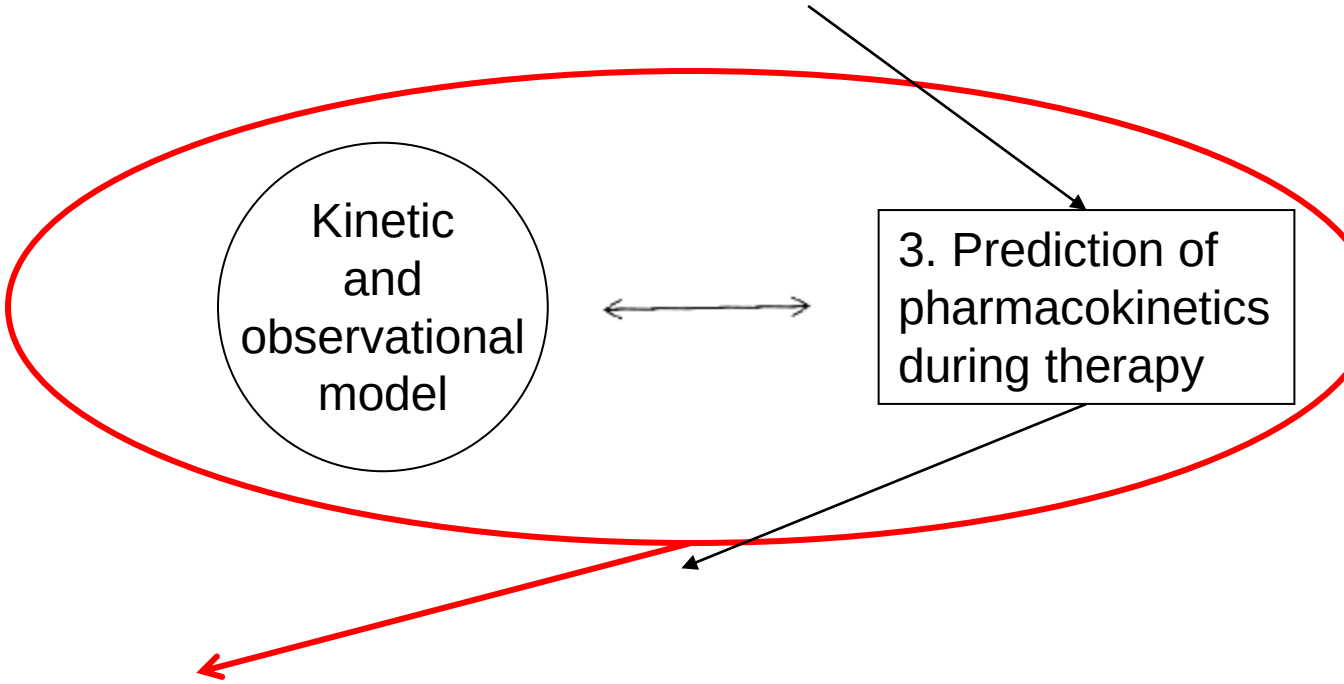
Advances

- Choosing optimal sampling scheme based on population kinetics

Challenges/Opportunities

- Increasing accuracy and precision of time-integrated activity coefficient (residence time) τ_j
- Reducing number of measurements and thus patient load
- Reduce radiation exposure due to imaging (if PET/CT)

3. Dosimetry for TRT: Flowchart



3.3 Modulation of Biodistribution

Standard

- lysine/arginine coinfusion to saturate kidney uptake by competitive inhibition (used for kidney protection in PRRT)

Advances

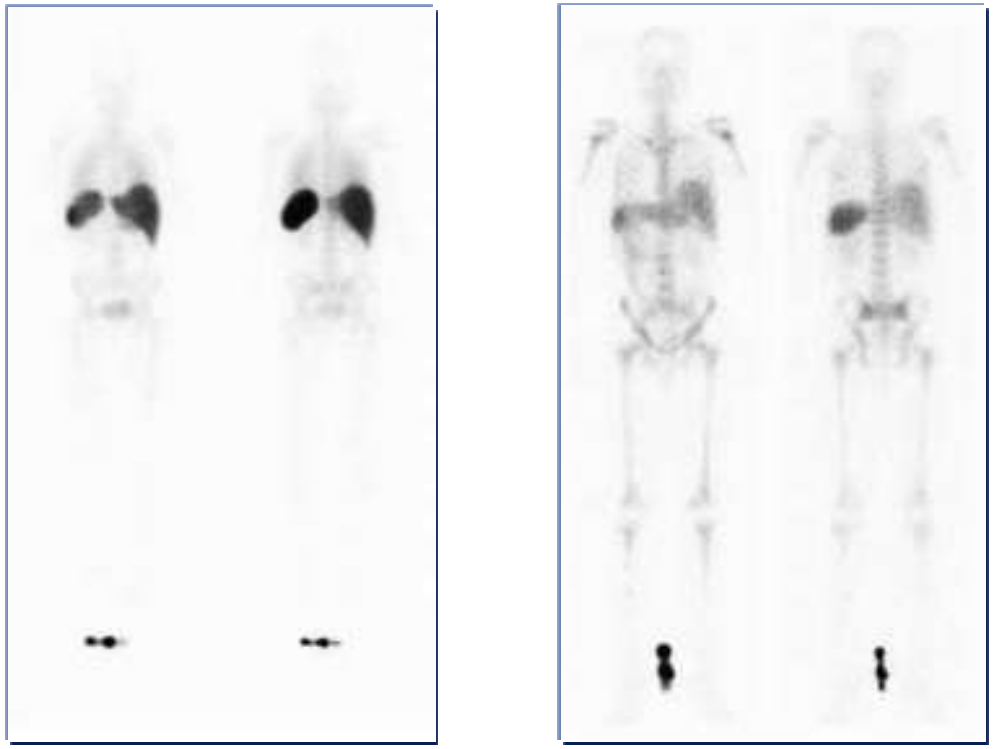
- **Individualized** preload (mab, peptides) and pretargeting

Challenges/Opportunities

- Same specific activity, radiopharmaceutical quality and nuclide purity
- Development of an adequate PBPK model is essential
- Fast simulations based on individual patient data yielding considerable improvement of biodistribution (factor in therapeutic ratio about 2)

software safety!

Modulation of Biodistribution: Example



without 0,5 mg/kg unlabelled mab with

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

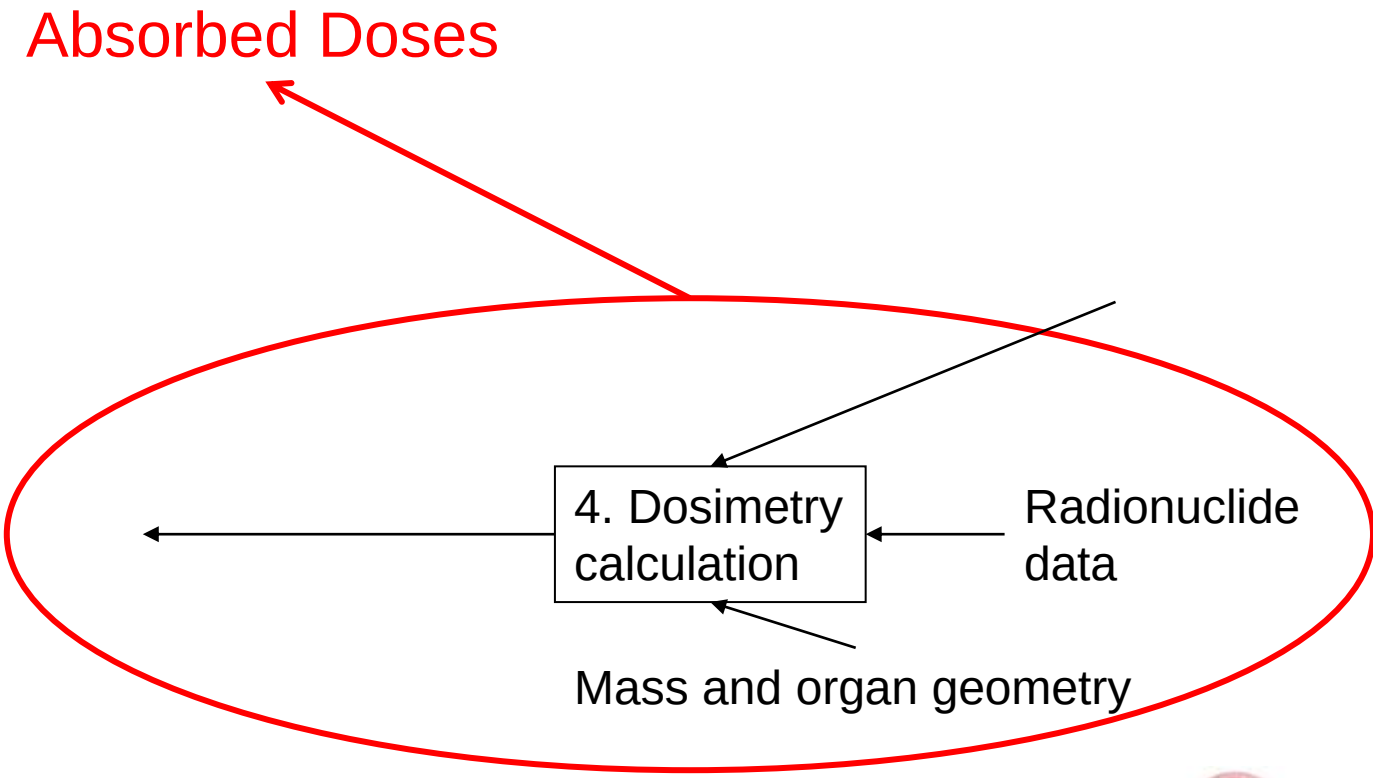
used for

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

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

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

3. Dosimetry for TRT: Flowchart



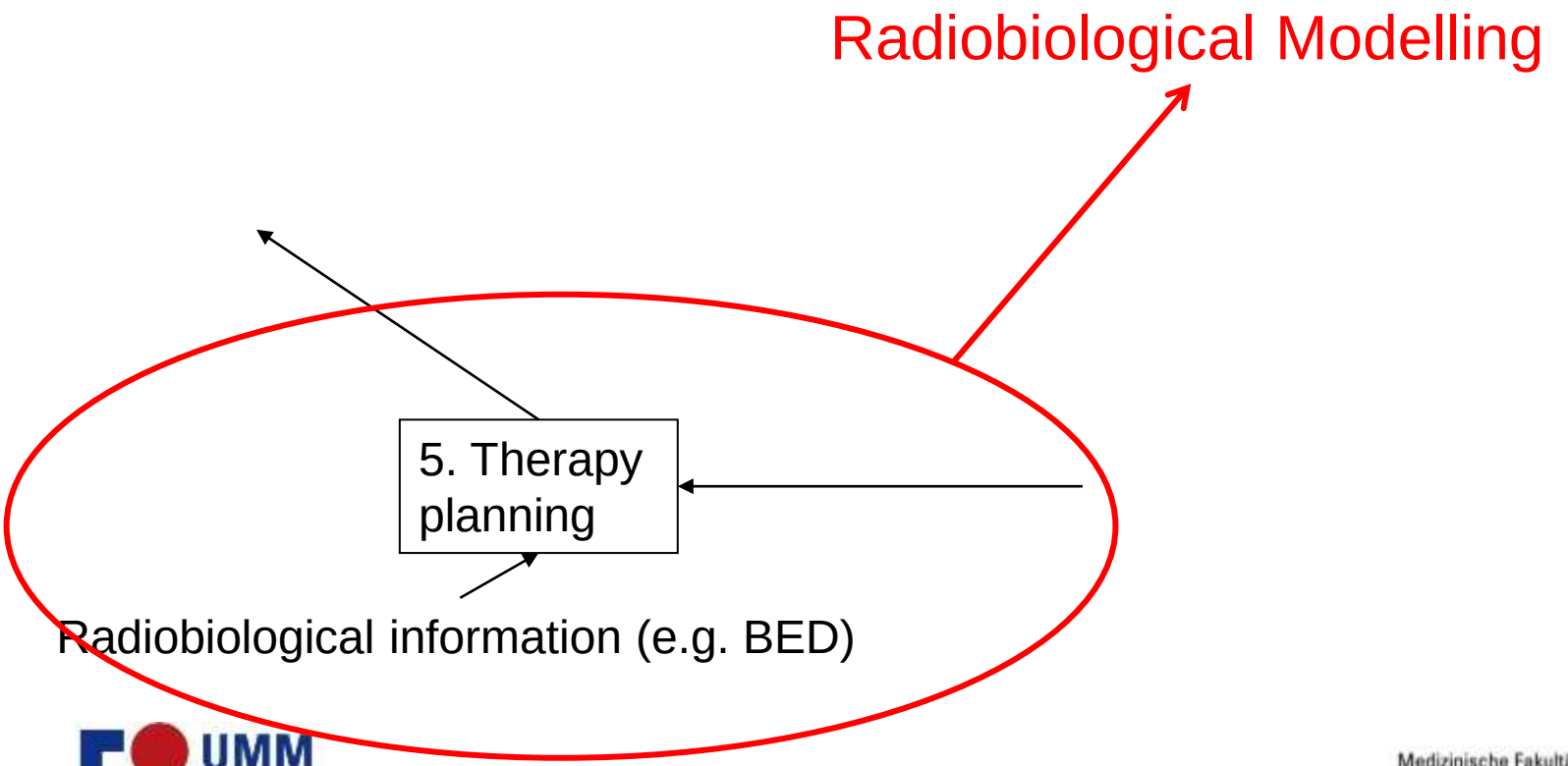
3.4 Absorbed Dose Calculation

Standard
- Whole-body / organ level
- Anthropomorphic phantom S factors => OLINDA software

Advances
- voxel / cellular level (inhomogeneities taken into account)
- individual S factors / convolution kernels / Monte-Carlo simulations
- Additional nuclides, e.g. α-emitter

Challenges/Opportunities
- Standardized procedure for defining the relevant dimension
- Benchmarking with respect to accuracy

3. Dosimetry for TRT: Flowchart



3.5 Radiobiological Modelling

Standard

- only physical dose prescription (max. dose (Gy) for risk organs)

Advances

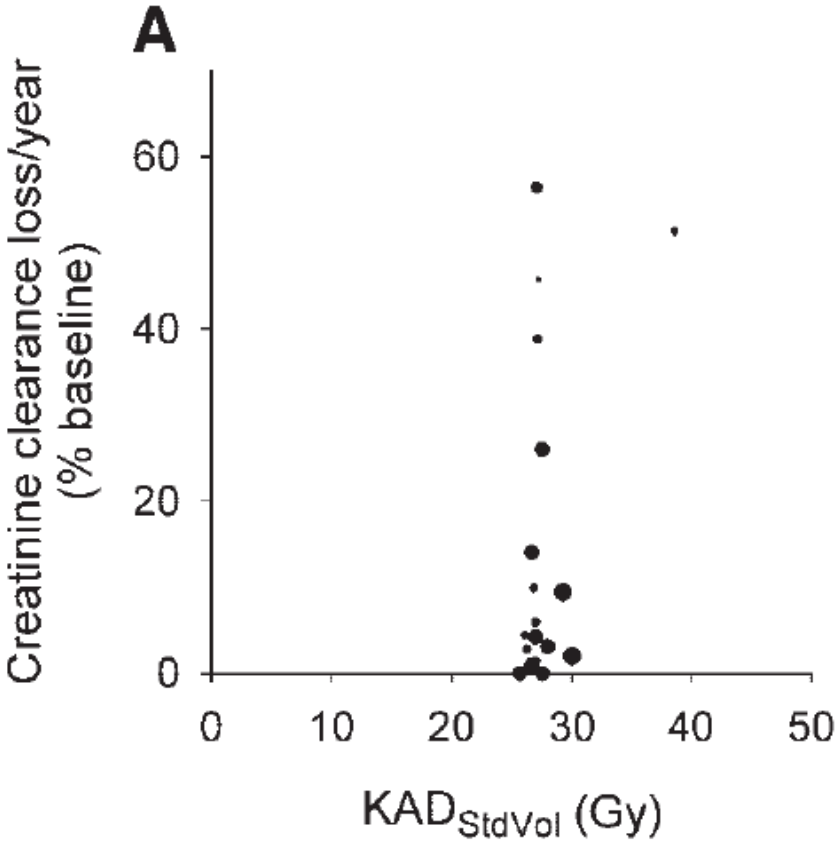
- incorporation of dose rate effect and DNA repair, linear-quadratic model with organ specific parameters α and β , biologically effective dose (BED), fractionation
- Inclusion of additional information (hypoxia, proliferation, angiogenesis) obtained from molecular imaging

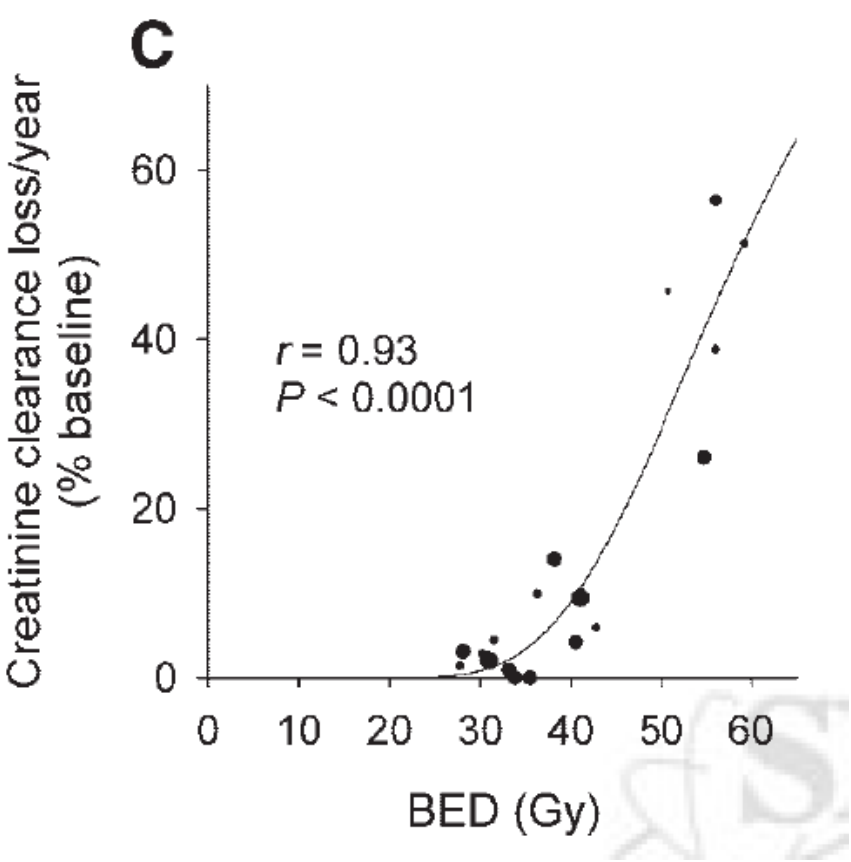
Challenges/Opportunities

- individualization will reduce the number of over- and under-treated patients

Biologically Effective Dose (BED): Kidneys

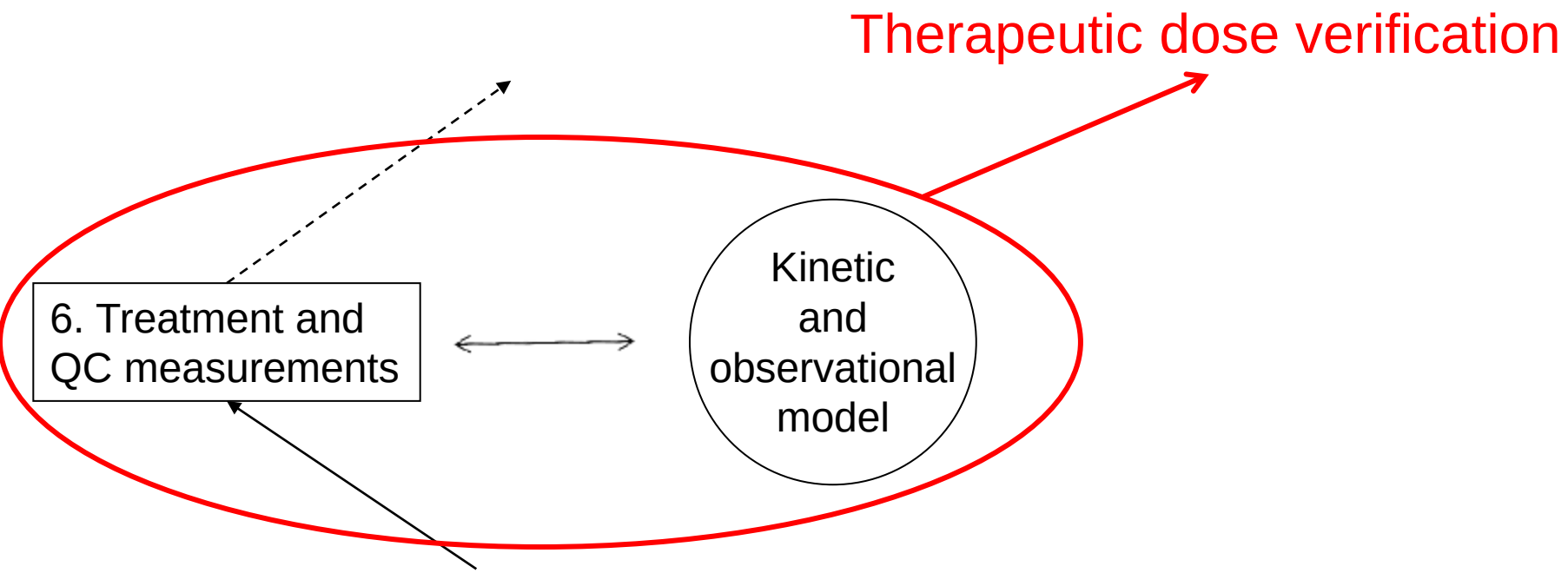
Dose-response relationship





Barone et al. J Nucl Med 2005

3. Dosimetry for TRT: Flowchart



3.6 Therapeutic Dose Verification

Standard

- (Radiopharmaceutical quality control)
- planar (^{90}Y, ^{213}Bi) or 3D imaging (^{131}I)

Advances

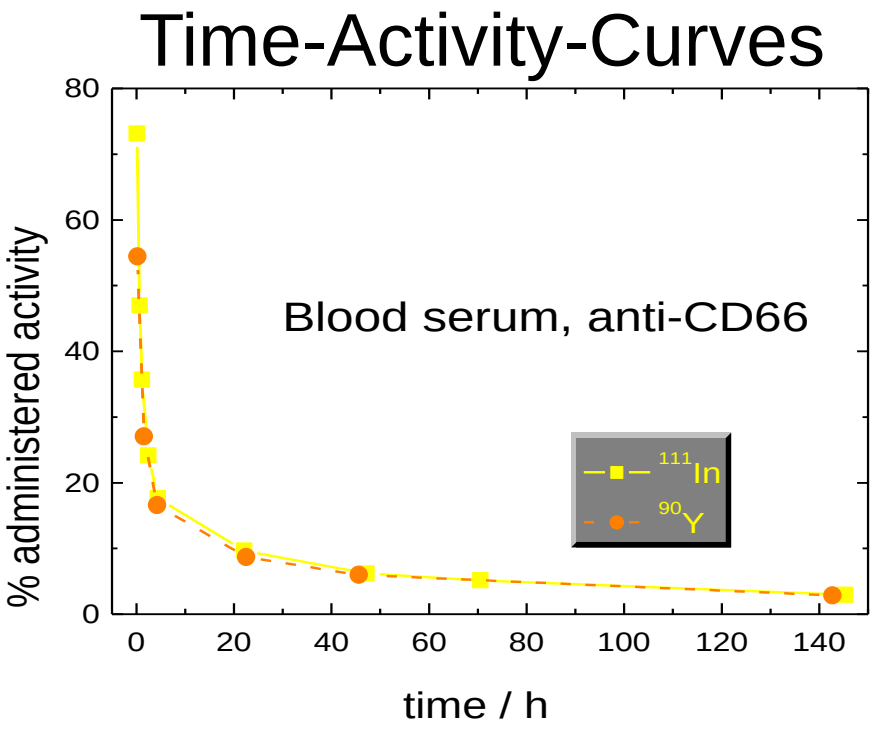
- development of routine dose control methods, e.g. image quantification of nuclides (Bremsstrahlung), serum kinetics + PBPK model, …

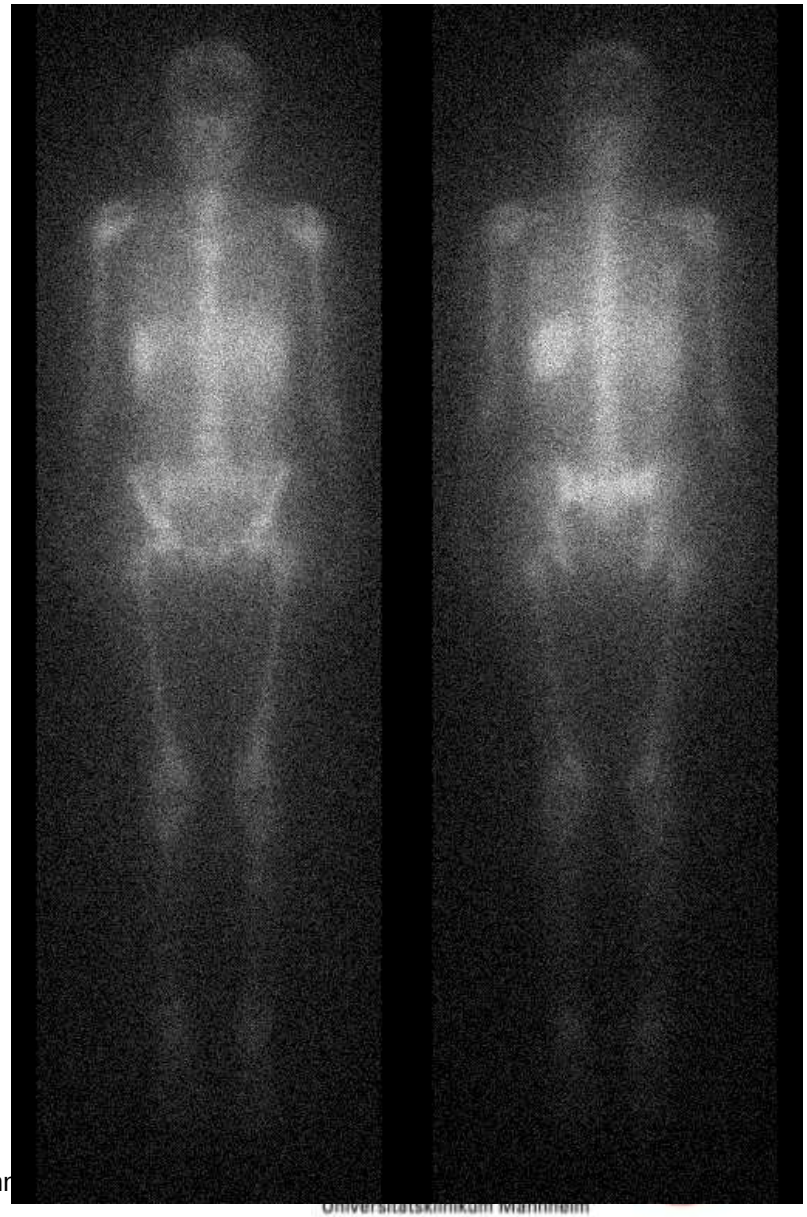
Challenges/Opportunities

- defining simple but effective methods for QC

Dose Verification

^{90}Y-anti-CD66, 24 h p.i.





Courtesy Prof. S.N. Reske, Nuclear Medicine Clinic, Ulm University, Germany

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4. Conclusion

Determination of individualized dosimetry-based activity is very sophisticated!

- Not every centre is (or will be) able to develop a new TRT!

However:

After development, the implementation in many centres should be achievable!

This depends on the complexity of the treatment, e.g. on

- Needed degree of individualization
- Available equipment
- Needed analyses

4. Conclusion: Suggested Efforts

- Standardization of dosimetric procedures
  - First: Standardized dosimetry reporting (Lassmann et al. 2011 EANM dosimetry committee)
- Defining standard operating procedures
- Development of methods for testing accuracy and reproducibility of all steps
- Development of procedures for quality management and quality assurance
  - Uncertainty reporting!

Federal Ministry of Education and Research

- Next stage: take into account in treatment planning the additional therapies the patient had or will have!

5. References

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