Outcome Prediction in Radiopharmaceutical Therapy Using PBPK/PD Modelling

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https://www.uniklinik-ulm.de/nuklearmedizin/en/nuclear-medicine/chair-of-medical-radiation-physics.html

Predicting Outcome (Toxicity) in Radiopharmaceutical Therapy
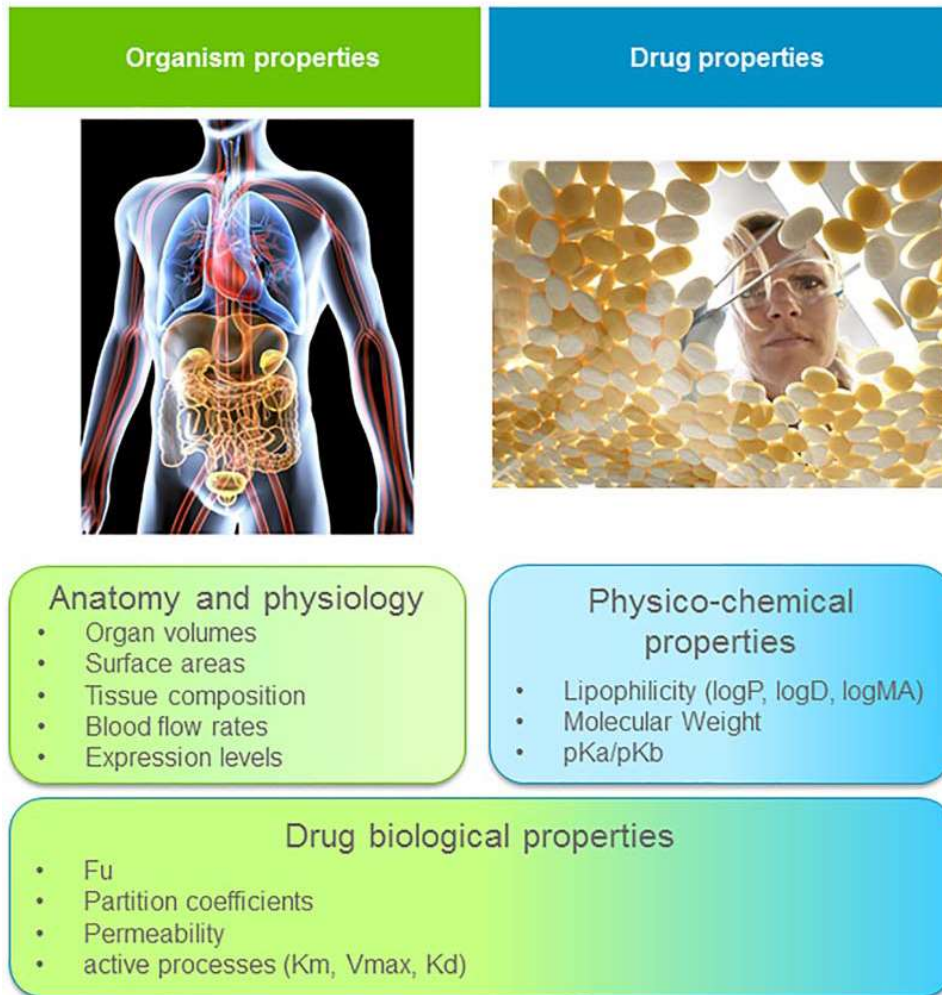
Two contributors in Radiopharmaceutical Therapy:

- Pharmacokinetics
    - „What the body does to the drug"

        Physiologically-based pharmacokinetic model

- Pharmacodynamics
    - „What the drug does to the body"

Physiologically-Based Pharmacokinetic (PBPK) Model

A priori knowledge …

Physiological models identify compartments with actual body spaces; actual transfer and flow rates are employed.

$\Rightarrow$ This can be descibed as a non-linear system of differential equations.
$\Rightarrow$ Implemented in a computer.
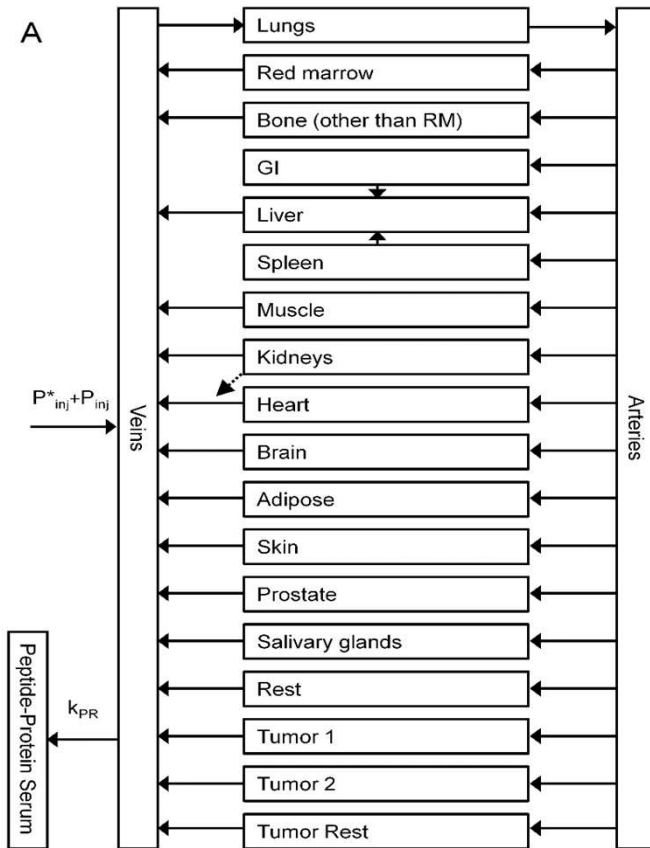
L Kuepfer et al. "Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model," CPT: Pharmacometrics Syst. Pharmacol. 2016
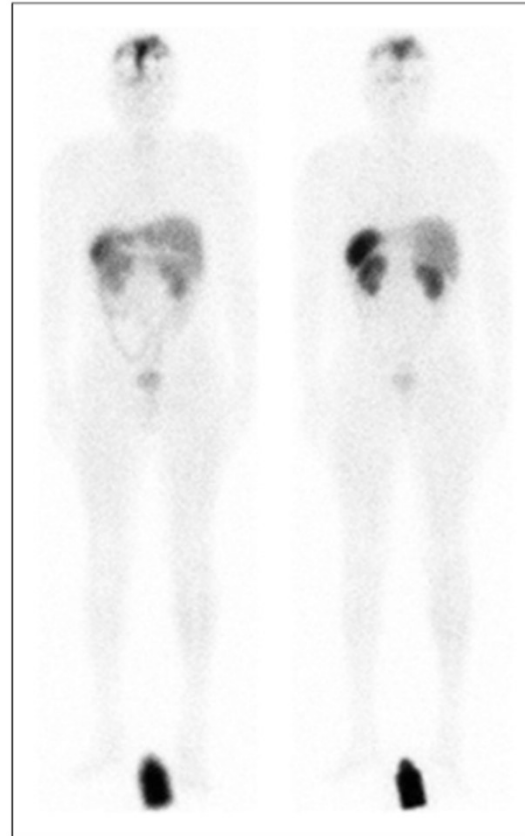
PBPK-Model   +   Individual Parameters   =   Virtual Patient

„in silico"

+

=   **Virtual NET patient**
^{177}Lu-DOTATATE

Can be used for
simulations and
predictions.

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        Radiobiological Model (Dose-Effect Relationship)

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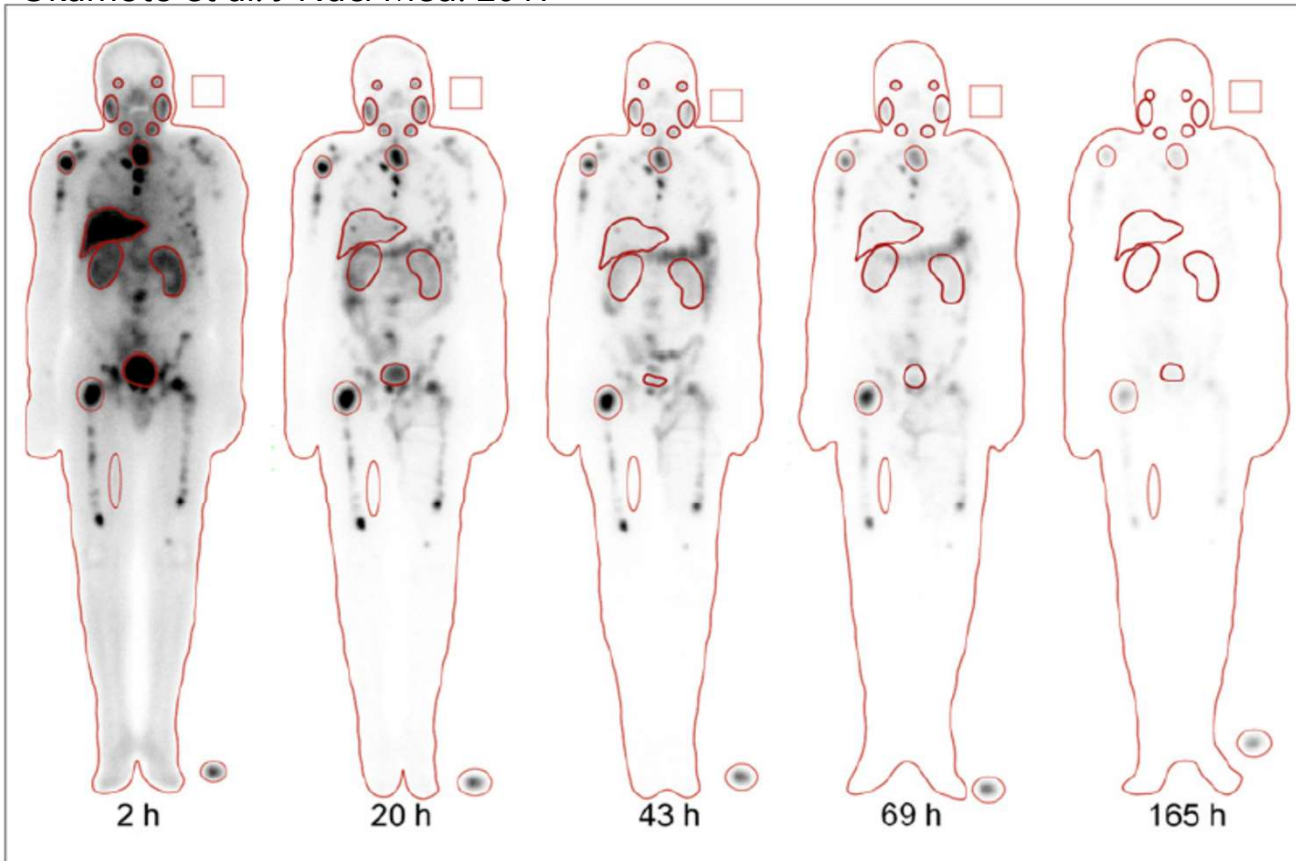# Radiobiological Model

Biologically effective dose (BED)

• Linear-quadratic model (alpha and beta parameters)

• Repair rate μ

• Tumour growth model

Strigari L, Konijnenberg M, Chiesa C, Bardies M, Du Y, Gleisner KS, *et al.* The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. *Eur J Nucl Med Mol Imaging* **2014**;41:1976-88

Example: ^{177}Lu-PSMA I&T

Okamoto et al. J Nucl Med. 2017

FIGURE 1. ^{177}Lu-PSMA I&T whole-body scintigraphy images obtained at 2, 20, 43, 69, and 165 h after administration. Regions of interest were drawn on liver, kidneys, parotid glands, submandibular glands, lacrimal glands, and lesions in right humerus, thoracic vertebrae, and right femur.
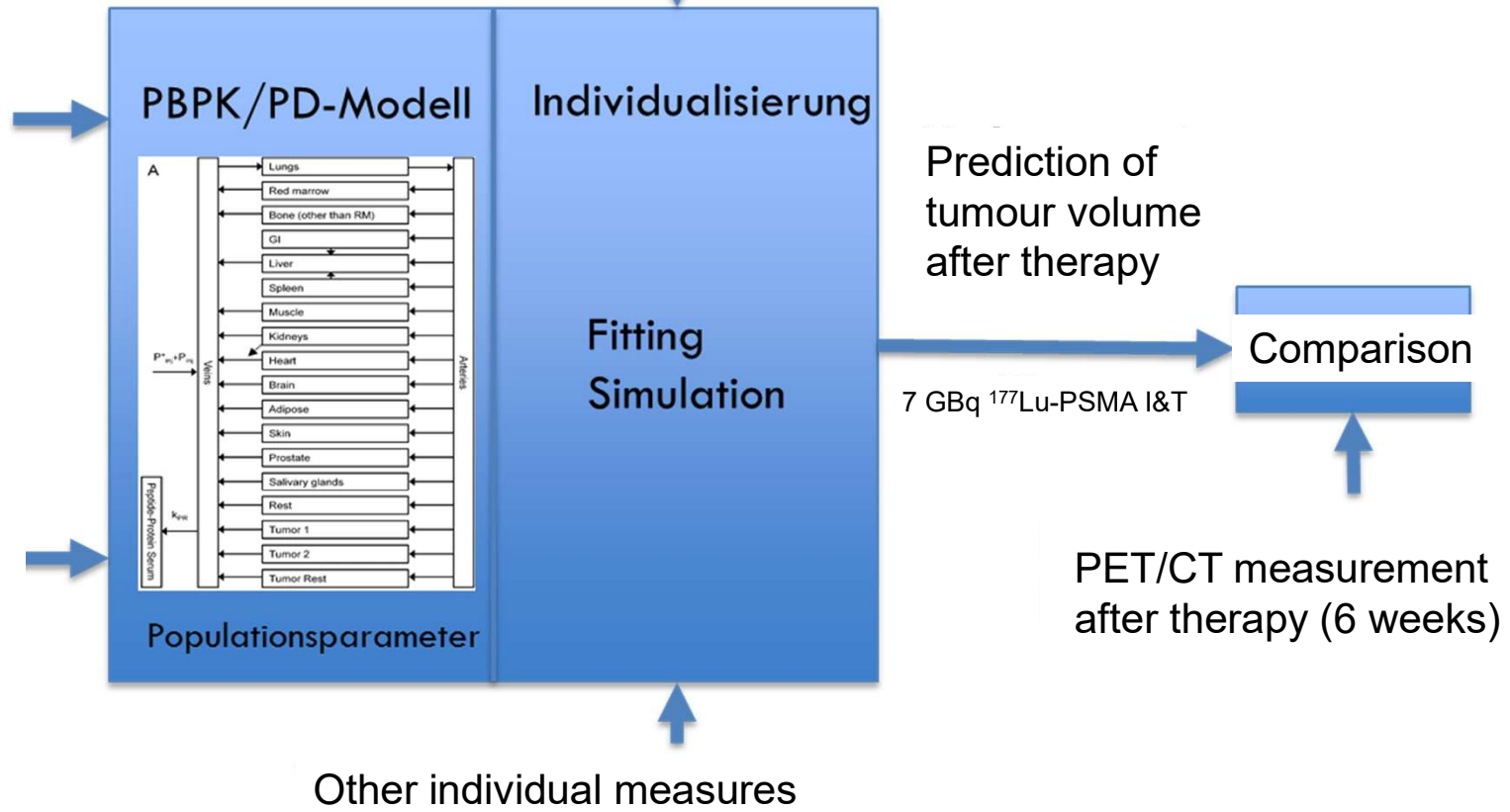
Metastatic Castration-Resistant Prostate Cancer

It would be good to identify in advance those patients who will not profit from the treatment
=> outcome prediction

2022

Modelling and Prediction of Tumour Response in RLT

PET/CT-Based „Outcome" Prediction (Tumour Volume)

Deviation   1% ± 40%

Normal tissue?

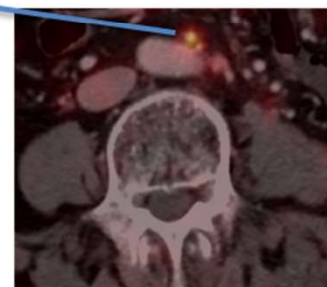Kletting P. et al. J Nucl Med. 2019;60:65-70.
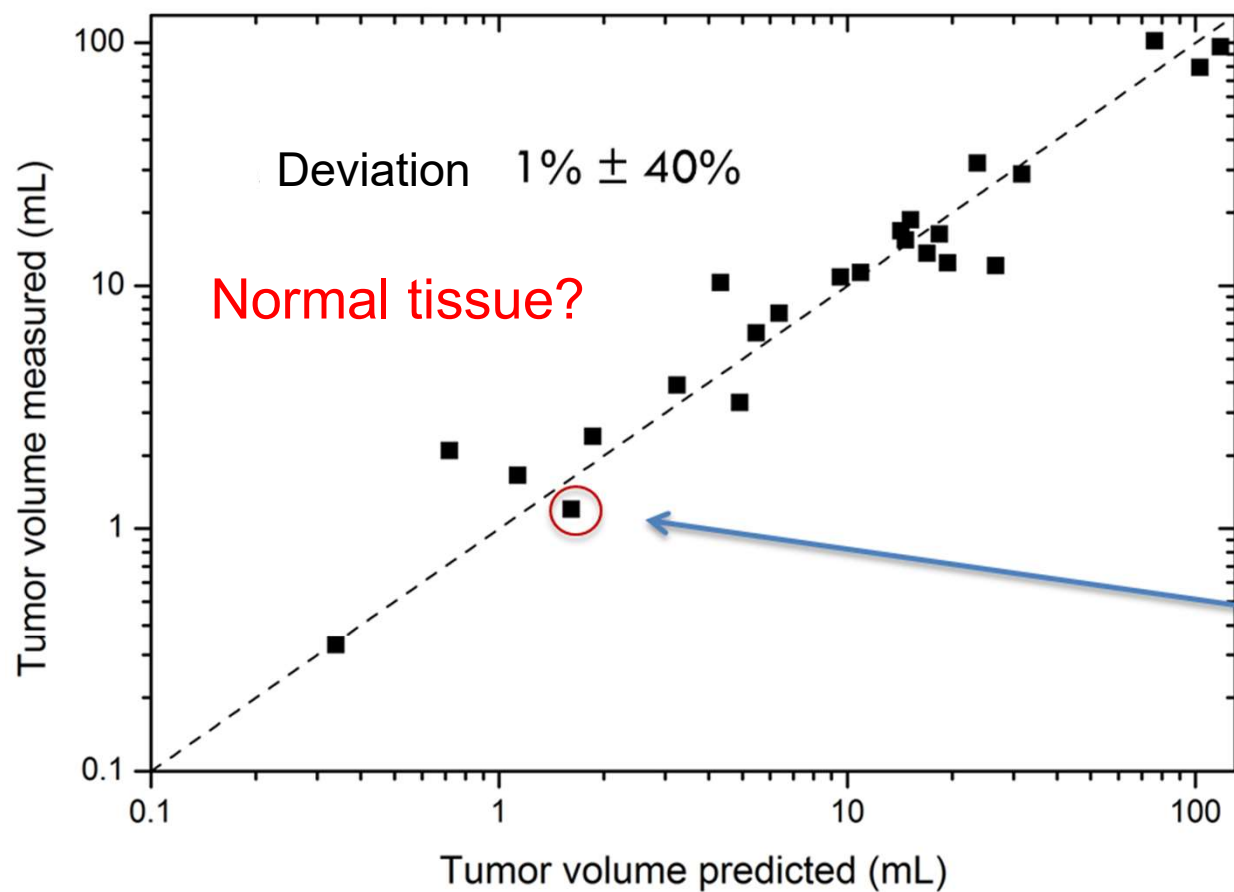
Summary:
- Combination of PK and PD
- Prediction good in average
- Improvements are needed
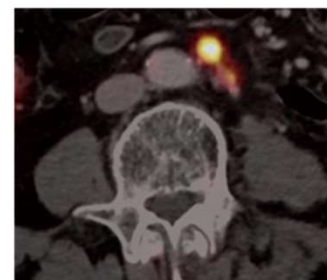
Before therapy

After therapy

Predicting **Kidney** Toxicity in Radiopharmaceutical Therapy

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    - „What the body does to the drug"

        Physiologically-based pharmacokinetic model $\Rightarrow$ Done

- Pharmacodynamics
    - „What the drug does to the body"

        Radiobiological Model (Dose-Effect Relationship)

        $\Rightarrow$ Needed