Modeling and predicting tumor response in radioligand therapy

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Running title: Predicting tumor response in RLT
ABSTRACT

The aim of this work was to develop a theranostic method that allows predicting PSMA-positive tumor volume after radioligand therapy (RLT) based on a pre-therapeutic PET/CT measurement and physiologically based pharmacokinetic/dynamic (PBPK/PD) modeling at the example of RLT using $^{177}$Lu-labeled PSMA for imaging and therapy (PSMA I&T). Methods: A recently developed PBPK model for $^{177}$Lu PSMA I&T RLT was extended to account for tumor (exponential) growth and reduction due to irradiation (linear quadratic model). Data of 13 patients with metastatic castration-resistant prostate cancer (mCRPC) were retrospectively analyzed. Pharmacokinetic/dynamic parameters were simultaneously fitted in a Bayesian framework to PET/CT activity concentrations, planar scintigraphy data and tumor volumes prior and post (6 weeks) therapy. The method was validated using the leave-one-out Jackknife method. The tumor volume post therapy was predicted based on pre-therapy PET/CT imaging and PBPK/PD modeling. Results: The relative deviation of the predicted and measured tumor volume for PSMA-positive tumor cells (6 weeks post therapy) was 1±40% excluding one patient (PSA negative) from the population. The radiosensitivity for the PSA positive patients was determined to be 0.0172±0.0084 Gy$^{-1}$. Conclusion: The proposed method is the first attempt to solely use PET/CT and modeling methods to predict the PSMA-positive tumor volume after radioligand therapy. Internal validation shows that this is feasible with an acceptable accuracy. Improvement of the method and external validation of the model is ongoing.
Keywords PBPK/PD model; radioligand therapy; $^{177}$Lu-PSMA; tumor response;
INTRODUCTION

Recently a number of studies have been published reporting the safety and efficacy of radioligand therapy (RLT) using $^{177}$Lu-labeled PSMA specific peptides for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) (1-4). Hematologic, renal parameters and changes in PSA levels were investigated in most studies (1-4). No study so far has investigated the relationship of the biologically effective dose (BED) and tumor volume changes. A dose-effect relationship is, however, a prerequisite for an improved therapy and adequate treatment planning. To establish such a relationship, a mathematical model, which describes, both, the pharmacokinetics and pharmacodynamics, i.e. tumor growth and radiation effect, is needed. With such a model, tumor volume changes could be predicted based on the injected activity (peptide amount and ligand properties). A first step towards that end was the development of a physiologically based pharmacokinetic (PBPK) model for $^{177}$Lu-labeled PSMA for imaging and therapy (PSMA I&T) (5-7). The next logical step is to link the BED to tumor reduction.

The aim of this work was to develop a theranostic method that allows predicting tumor volume after radioligand therapy based on a pre-therapeutic PET/CT and a PBPK/PD model. The model was developed using data (including PET/CT and planar images) of 13 patients with mCRPC treated with $^{177}$Lu-PSMA I&T. A recently published PBPK model (7) was extended with a tumor growth and linear quadratic model. Pathophysiological and radiobiological parameters for 26 tumor lesions were estimated in a Bayesian framework (8). The Jackknife method (9,10) was employed
for internal validation. The prediction accuracy of the model was determined by comparing the predicted and measured tumor volume 6 weeks post therapy. The prediction was based on the pre-therapy PET/CT image and PBPK/PD modeling.
METHODS

Patient Data

The patient data have been described elsewhere (4). In brief, the data of 13 patients (5) with mCRPC were included (4). All patients underwent the first cycle $^{177}$Lu-PSMA I&T RLT. The patients received 91.0±5.0 nmol PSMA I&T labeled with 7.3±0.3 GBq of $^{177}$Lu. The mean age and body surface area were 70±6 years and 2.0±0.12 m$^2$, respectively. The institutional review board of the Technische Universität München approved the compassionate use of $^{177}$Lu-PSMA I&T in mCRPC patients without other therapy options. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this retrospective study, informed consent was obtained from all individual participants and the retrospective analysis of the data was approved by the Ethics Committee of the Technical University Munich.

Planar Therapeutic Imaging and Image Processing

Planar whole body scintigraphy was performed as described previously (4). Two tumor lesions per patient with high uptake showing no considerable overlap with other tissue, i.e. other lesions or high physiological uptake, were investigated. In total, 20 bone and 6 soft tissue metastases were analysed (Table 1). The activity in the tumor region of interest included contributions from actual tumor and activity of the
underlying muscle or adipose tissue. PBPK modeling was used to correct for underlying tissue activity ((5) and Supplement B, equation B.1). Three patients underwent post-therapy scintigraphy at 5 time points, 1 patient at 4 time points and 9 patients at 3 time points (5). For this study time activity data of the kidneys, tumor and total body were used (Supplement B, table B.1).

**PET/CT Imaging and Image Processing**

$^{68}$Ga-PSMA-HBED-CC PET/CT for pre- and post-therapeutic staging was performed as described previously (4,11). The average injected amount of PSMA HBED-CC and $^{68}$Ga activity was 1.6±0.3 nmol and 115±16 MBq, respectively. The PET/CT image before therapy was used to determine the tumor volume and the fraction of injected activity required for fitting. For tumor volume determination SyngoVia (Syngo MMWP, Siemens Healthcare, Erlangen, Germany) was used. To estimate the volume of a single lesion and to determine the fraction of the tumor volume with PSMA-positive cells a volume-of-interest with a 20-50% of SUV$_{\text{max}}$ isocontour adjusting the volume-of-interest optimal to the anatomical configuration of the lesion was drawn (4). The post processing software application TrueD (Siemens Healthcare, Erlangen, Germany), was employed to derive the activity concentration of the kidney and two tumor lesions (tumor 1, tumor 2). Background activity correction was conducted within the PBPK model (supplement B, equations B.2-3).
The activity and volume of all other tumor lesions – named REST tumor in the following – were obtained by adding up all lesions slice by slice as described in supplement B, equation B.4.

**PBPK Model Structure**

SAAMII and Popkinetics (12) (version 2.2, The Epsilon Group, Washington, USA) were employed for modeling and fitting. For the pharmacokinetic part of the model, a recently developed whole-body PBPK model was applied (5,6). The PBPK model includes all relevant biological mechanisms such as blood flow, diffusion, PSMA specific binding and internalization as well as excretion.

**Tumor Effect Model**

Tumor growth and reduction was modeled using exponential growth and the linear quadratic model for the surviving fraction. Considering the slow net growth rates for PCa and the time interval between the pre-therapeutic PET/CT and therapy (≤ 3 weeks in 11 out of 13 patients) and post-therapy PET/CT (6 weeks) simple exponential growth is a good approximation to Gompertzian growth or other growth models. The volume of the tumor $V_{TU, total, 0}$ was thus described:

$$V_{TU, total}(t) = V_{TU, total, 0} \cdot e^{(\lambda \cdot t - \alpha_{TU} \cdot BED_{TU})}$$

(1)

$$BED_{TU} = D_{TU} \cdot (1 + \frac{G_{TU}}{\alpha_{TU} / \beta_{TU}} \cdot D_{TU})$$

(2)
$t$ is the elapsed time starting from the pre-therapeutic PET/CT, $V_{TU,\text{total},0}$ is the volume of the first PET/CT, $\lambda_g$ the net growth rate (bone lesions: $5.1 \cdot 10^{-6}$ min$^{-1}$, soft tissue lesions: $3.8 \cdot 10^{-6}$ min$^{-1}$) as reported by Berges et al. (13) for androgen independent cells, $BED_{TU}$ the biologically effective dose and $\alpha_{TU}$ the intrinsic radiosensitivity of PSMA-positive tumor cells. The radiosensitivity $\alpha_{TU}$ is fitted. It represents rather an effective value as it is not known to which extent radiation (lethally) damaged cells still express PSMA until they die.

The volumes determined by the post-therapy PET/CT were included as measurement data (assuming a relative error of 10%) for the fitting process. The elapsed times from the first PET/CT to therapy and to the second PET/CT were 8-63 d and 38-42 d, respectively (Table 1). The $\alpha_{TU}/\beta_{TU}$ ratio ($1.49$ Gy$^{-1}$) and repair rate $\mu_{TU}$ ($0.0061$ min$^{-1}$) were assumed to equal those determined for brachytherapy for primary prostate cancer (14) and were incorporated as fixed values. The Lea-Catcheside factor $G$ of each tumor lesion was numerically determined within the PBPK model according to (15):

$$G_{TU}(T) = \frac{2}{D_{TU}^2} \cdot \int_0^T \hat{D}_{TU}(t) \, dt \cdot \int_0^T \hat{D}_{TU} (\omega) \cdot e^{-\mu_{TU}(t-\omega)} \, d\omega$$  (3)

For the calculation of the absorbed dose only the self-dose was considered

$$\hat{D}_{TU}(t) = A_{TU}(t) \cdot S_{TU-TU} = A_{inj} \cdot a_{TU}(t) \cdot S_{TU-TU}$$  (4)

$$D_{TU}(T) = \int_0^T \hat{D}_{TU}(t) \, dt = A_{inj} \cdot \tilde{a}_{TU}(T) \cdot S_{TU-TU}$$  (5)
The dose factors for the tumor lesions were derived from OLINDA/EXM (16) data as described in supplement A, Table B. The dose factors were assumed to be constant during therapy.

**Population Fitting**

For parameter estimation, an iterative fitting approach (Fig. 1) (9) was employed. To determine the population parameters, the model parameters for each patient were simultaneously fitted to 1) the activity concentration of the pre-therapeutic PET 2) the time activity data during therapy 3) and the tumor volumes. Thus, 10 adjustable parameters (with Bayesian term) were fitted to a minimum of 17 data points. Tumor growth (exponential) and reduction (linear quadratic model), different peptide properties (e.g. molecular size) and injected amounts for PET/CT and therapy were taken into account.

For internal validation the leave-one-out Jackknife method was employed. For that purpose 13 population parameter distributions were determined using the method described above leaving out one patient each time. The quality of the fits were checked according to (17).

**Individual Fitting and Prediction Accuracy**

To internally validate the prediction power of the model, for each patient the predicted and the actual tumor volume were compared. For that, the blood flow and receptor density of each individual patient (7 parameters) were fitted with Bayesian information (of the 12 other patients) solely to the pre-therapeutic PET/CT data (1
data point per investigated region of interest). The release rates and the radio sensitivity $a_{TU}$ were fixed to the mean value of the leave-one-out population parameter. Fitting in a Bayesian framework allows having more adjustable parameters than number of samples.

Thus, the predictions of the post-therapy tumor volume was based on the PBPK/PD model, the population parameters of the 12 other patients (as Bayesian information) and the pre-therapeutic PET/CT of each patient. The prediction accuracy of the tumor volume was defined as the relative deviation, $RD$, of the simulated and measured tumor volume, $V_{TU,\text{total PETCT2}}$, after therapy at the time of the second PET/CT, $t_{PETCT2}$.

$$RD_{TU,\text{Volume}} = \frac{V_{TU,\text{total}} \cdot e^{(\gamma f_{PETCT2} - a_{TU} BED_{TU})} \cdot V_{TU,\text{total PETCT2}}}{V_{TU,\text{total PETCT2}}} \cdot 100\%$$  \hspace{1cm} (6)

### Predicted BEDs and tumor volume changes

The BED was predicted using the PBPK/PD model, the jackknife population parameters (including the $a_{TU}$) and the pre-therapy PET/CT data. To demonstrate the relationship of tumor volume reduction and BED, the predicted relative reduction of the tumor volume was calculated for each lesion. The tumor volume at the beginning of therapy was used as reference point, to normalize for varying time intervals between the pre-therapeutic PET and therapy.
RESULTS

Population Fitting

The radiosensitivities $\alpha_{\text{TU}}$ provided in Table 2 show the averaged values and pertaining standard deviations (leaving out the corresponding patient) after convergence of the iterative fitting process. The Jackknife method showed that patient 7 (PSA negative) considerably changed the population values (Table 2). Thus this patient was removed and in a second step the Jackknife method was again applied to the reduced population. The average radiosensitivity $\alpha_{\text{TU}}$ of the 13 investigated patients and the population without patient 7 was estimated to be $0.022\pm0.022 \text{ Gy}^{-1}$ and $0.0172\pm0.0084 \text{ Gy}^{-1}$, respectively. For the reduced patient population, visual inspection showed excellent fits, except for patient 5, tumor 2. The coefficient of determination $R^2$ (Supplement C, Table 2) was $>0.8$ for all curves in all patients, except for patient 5, tumor 1 ($R^2 = 0.77$) and tumor 2 ($R^2 = 0.40$), and for patient 3, total body ($R^2 = 0.73$). A typical fit and the one with the lowest $R^2$ are depicted in Supplement C, Fig. C.1. All fits yielded coefficients of variation (relative standard errors) $<50\%$ for any estimated parameter, except $\alpha_{\text{TU}}$ of patient 3 (52%) and 9 (56%). Elements of the correlation matrix were between -0.76 and 0.71. The values of the estimated parameters are in a physiologically reasonable range i.e. comparing favorably to literature values (Supplement C, Table 1).

Individual Fitting and Prediction Accuracy
Visual inspection showed excellent fits. The coefficients of variation were < 27% for all blood flows and < 71% for the tumor receptor densities. Elements of the correlation matrix were between -0.88 and 0.71.

The mean relative deviation of the measured and predicted tumor volume in the investigated population (without P7) was determined to be 1±40% (Table 2 and Fig. 2).

**Predicted BEDs and tumor volume changes**

Table 2 shows the BEDs, the tumor volumes at the beginning of therapy and the predicted tumor volumes 6 weeks after therapy. The relationship between the predicted BED and the predicted tumor volume reduction after therapy is depicted in figure 3.
DISCUSSION

In this work, we developed a method to predict PSMA-positive tumor volume after $^{177}$Lu-PSMA I&T RLT using the pre-therapeutic PET/CT and a PBPK/PD model. Data of 13 patients with mCRPC were used. Pharmacokinetic parameters and the radiosensitivity $\alpha_{TU}$ were estimated employing a PBPK/PD, the time activity data (PET/CT and planar images) and tumor volumes of 13 patients (26 tumor lesions). Data from literature values for growth of androgen-independent prostatic cancer cells (13) and radiobiological parameters ($\alpha_{TU}/\beta_{TU}$ and $\mu_{TU}$) known from brachytherapy (14) were used. The values obtained (PSA positive patients) for radiosensitivity $\alpha_{TU}$ (0.0172±0.0084 Gy$^{-1}$) are 2.3-fold lower than the mean values determined for primary tumor brachytherapy (14). For internal validation the leave-one-out Jackknife method was employed. The difference of the measured and predicted PSMA-positive tumor volume (accessible to the peptide) was 1±40 % excluding the PSA negative patient. In this patient the radiosensitivity $\alpha_{TU}$ was considerably larger (0.068 Gy$^{-1}$).

Here, planar imaging was used to identify population parameters, which were then included as Bayesian or fixed parameters for individual fitting, prediction and validation. Population parameters were obtained by simultaneously fitting of 3D (pre-therapeutic PET/CT) and 2D (planar) data in combination with sophisticated corrections methods. The more accurate PET/CT allowed correcting data for the first hours of uptake, while the information for later time points solely stems from planar imaging. Therefore, we believe that the release rates may represent the most uncertain parameters. Undoubtedly, it would be desirable to have population values with lower
standard deviations. This could be achieved with measurements that are more accurate and with the creation of subpopulations depending for example on the PSA level.

Therefore, the focus of future work regarding this herein presented model approach should be on 1) analyzing a larger patient group in whom SPECT/CT imaging was conducted and 2) including more \textit{a priori} information of each individual. Planar imaging during therapy is still standard practice although SPECT/CT data might improve the accuracy of the estimated pharmacokinetic parameters. Although we have included 3D information using the pre-therapeutic PET/CT for the fitting process, using 3D imaging during therapy more lesions per patient can be investigated, as the PBPK model allows correcting for overlaying normal tissue but not for other lesions. More soft tissue lesions would be desirable, as it is inherently challenging to determine volume changes in bone metastases. However, using both, the PET and the CT information reduced the inaccuracy. An error of 10\% to account for this uncertainties arising was assigned. Further error in the calculation of the absorbed dose and BED is introduced by assuming the tumor being a sphere, the same radiobiological parameters for all lesions and a constant growth rate over the whole time period. SPECT/CT data during therapy will help to reduce the number of assumptions. However, based on our results it can be concluded that the assumptions made in this study were useful for the investigated population.

Furthermore, we conducted the population study including patients with a large variation in PSA levels. The prediction accuracy would probably further increase using subpopulations with similar PSA levels and treatment histories. More
sophisticated tumor dynamic models including compartments for various conditions of tumor cells (vital, necrotic, lethally damaged) (18) might improve the overall understanding of the treatment effects and the relationships of the radiosensitivity and PSA or perhaps the overall tumor load.

As this work focus on the tumor dose-effect relation, we did not define a clinical endpoint for dose effect on the kidneys and salivary glands. Future work will include treatment effect for normal tissue. Before applying this approach for a full \textit{in silico} clinical trial, further validation and extension of our model is needed investigating the link between a PBPK/PD model and clinical outcome parameters (e.g. overall survival). External validation, using the model and the population parameters to predict the volume changes in a different patient group, is planned.
CONCLUSION

We present a novel method to model and predict tumor response in radioligand therapy. The volume of PSMA-positive tumor tissue (6 weeks post therapy) was predicted based on the pre-therapeutic PET/CT and a PBPK/PD model. The relative deviation of the predicted and measured tumor volume was 1±40%. Future work including a refined model, definition of subpopulations and use of SPECT/CT data will help to improve further the prediction accuracy of the model.

DISCLOSURE

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

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REFERENCES


**Figure legends**

**Patient individual data N-1**
- Demographic data
- Organ and tumour volumes (PET/CT) before and after therapy
- Time activity data (PET/CT and gamma camera)

**Population parameters**
- Fixed (literature)

**Model structure**
- Pharmacokinetics: PBPK
- Pharmacodynamics: BED

**Properties of radioligands**
- Peptides: affinity, etc.
- Radionuclides: half-life, etc.
- Injected activities and amounts

**Fitting of model to volumes and time activity data**
- *i*th patient excluded

**Parameter distribution for the population**
- *i*th patient excluded

**Converged?**
- no
- yes

**Fitting of model to time activity data of *i*th patient**

**Prediction of tumor volume of patient *i***

**Comparison of predicted and measured tumor volume of *i*th patient**

**FIGURE 1.** Model fitting and prediction of tumor volume after treatment. An iterative fitting approach was used to determine Bayesian parameters for the investigated population. Based on the PBPK model, the population parameters (as fixed or Bayesian information) and the pre-therapeutic PET of the excluded patient, the volume after treatment was predicted and compared to the measured values. This was conducted for all (*N*=13) patients.
FIGURE 2. Predicted versus measured tumor volume. The prediction is based on the PBPK/PD model, the pre-therapeutic measurement and the population parameters.
FIGURE 3. Predicted tumor volume reduction versus predicted BED. The predictions are based on the PBPK/PD model, the pre-therapeutic measurement and the population parameters. A clear dose-effect (i.e. BED-volume change) relationship is visible. Note that for each patient a different radiosensitivity was used. In addition, for bone and soft tissue metastases different growth rates were assumed.
<table>
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<th>PET/CT Tumor volume (ml)</th>
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*LN = Lymph node
### TABLE 2

Predicted therapeutic and post-therapeutic quantities based on the pre-therapy PET/CT

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<th>Patient no.</th>
<th>RD* (%)</th>
<th>αTU* (Gy⁻¹)</th>
<th>D* Predicted† (Gy)</th>
<th>BED* Predicted† (Gy α/β)</th>
<th>VTU,Tumor* (ml)</th>
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<td>17</td>
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<tr>
<td>P4</td>
<td>−4.7</td>
<td>10</td>
<td>0.0152±0.0066</td>
<td>15</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>P5</td>
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<td>13</td>
<td>0.0186±0.0080</td>
<td>19</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>P6</td>
<td>30</td>
<td>23</td>
<td>0.0172±0.0090</td>
<td>6.6</td>
<td>6.2</td>
<td>7.7</td>
</tr>
<tr>
<td>P7</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>P8</td>
<td>49</td>
<td>28</td>
<td>0.0165±0.0086</td>
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<td>20</td>
<td>31</td>
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<tr>
<td>P9</td>
<td>−26</td>
<td>−15</td>
<td>0.0187±0.0076</td>
<td>13</td>
<td>11</td>
<td>17</td>
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<tr>
<td>P10</td>
<td>−23</td>
<td>−15</td>
<td>0.0182±0.0086</td>
<td>17</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>P11</td>
<td>3.0</td>
<td>−32</td>
<td>0.0182±0.0086</td>
<td>17</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>P12</td>
<td>−3.9</td>
<td>−12</td>
<td>0.0174±0.0090</td>
<td>15</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>P13</td>
<td>−58</td>
<td>−66</td>
<td>0.0163±0.0083</td>
<td>24</td>
<td>39</td>
<td>36</td>
</tr>
</tbody>
</table>

| Mean       | 1       | 0.0172      | 17.7 | 26 | 21 | 21 | 21 | 13 | 19 |
| SD         | 40      | 0.0084      | 6.9 | 14 | 25 | 30 | 19 |

*RD = relative deviation of predicted and measured tumor volumes 6 weeks after therapy; αTU = radiosensivities estimated using populations fits and Jack-knife method for PSA positive patients; D = absorbed dose; BED = biologically effective dose; VTU,Tumor = tumor volume; Reduction = predicted reduction for 6 weeks after therapy relative to the beginning of therapy; T1 and T2 = tumor 1 and tumor 2.

†Predicted = these values were determined (for the beginning of therapy and 6 weeks post therapy) using the pre-therapeutic PET/CT and the PBPK/PD model.
A. Equations, parameters and compartments

PBPK model equations

The following equations describe the transport of labelled (indexed with *) and unlabelled peptide via blood flow, extravasation, binding, internalization, degradation and release, excretion and radioactive decay. For therapy the peptide was intravenously injected as a 20 min infusion. The PET tracer was injected as a bolus. The variables are defined in Table A.1.

**Bound and internalized peptide:**

Parotid, submandibular and lacrimal glands, tumour, kidneys, liver, spleen, GI and prostate:

Constraint for total PSMA receptors $R_{0,i}$ (saturable binding)

$$R_{0,i} = R_i + RP_i + RP_i^*$$  \hspace{1cm} (1)

Internalized peptide

$$\frac{d}{dt} P_{\text{intern,}} = \lambda_{\text{int,}} \cdot RP_i - \lambda_{\text{release,}} \cdot P_{\text{intern,}} + \lambda_{\text{phy,}} \cdot P_i^*$$  \hspace{1cm} (2)

Bound peptide on cell surface

$$\frac{d}{dt} RP_i = k_{\text{on,}} \cdot P_{\text{int,}} \cdot \frac{R_i}{V_{\text{int,}}} - (k_{\text{off,}} + \lambda_{\text{int,}}) \cdot RP_i + \lambda_{\text{phy,}} \cdot RP_i^*$$  \hspace{1cm} (3)
Free peptide, vascular:

Transcapillary extravasation is described by the permeability surface product ($PS_i$) and the vascular ($V_{i,v}$) and interstitial volumes ($V_{i,int}$) of the pertaining tissue. Convection from the vascular to the interstitial space is neglected as the used peptide represents a rather small molecule ($I$).

All tissues except kidneys and lungs

$$\frac{d}{dt} P_{i,v} = PS_i \left( \frac{P_{i,int}}{V_{i,int}} - \frac{P_{i,v}}{V_{i,v}} \right) + F_i \left( \frac{P_{ART}}{V_{ART}} - \frac{P_{i,v}}{V_{i,v}} \right) + \lambda_{phy} \cdot P_{i,v}^*$$

$$\frac{d}{dt} P_{i,v}^* = PS_i \left( \frac{P_{i,int}}{V_{i,int}} - \frac{P_{i,v}^*}{V_{i,v}} \right) + F_i \left( \frac{P_{ART}}{V_{ART}} - \frac{P_{i,v}^*}{V_{i,v}} \right) - \lambda_{phy} \cdot P_{i,v}^* \tag{4}$$

For brain $PS = 0$

Lungs

$$\frac{d}{dt} P_{LU,v} = PS_{LU} \left( \frac{P_{LU,int}}{V_{LU,int}} - \frac{P_{LU,v}}{V_{LU,v}} \right) + F \left( \frac{P_{VEN}}{V_{VEN}} - \frac{P_{LU,v}}{V_{LU,v}} \right) + \lambda_{phy} \cdot P_{LU,v}^*$$

$$\frac{d}{dt} P_{LU,v}^* = PS_{LU} \left( \frac{P_{LU,int}}{V_{LU,int}} - \frac{P_{LU,v}^*}{V_{LU,v}} \right) + F \left( \frac{P_{VEN}}{V_{VEN}} - \frac{P_{LU,v}^*}{V_{LU,v}} \right) - \lambda_{phy} \cdot P_{LU,v}^* \tag{5}$$

Kidneys
\[
\frac{d}{dt} P_{K,v} = -\frac{P_{K,v}}{V_{K,v}} \cdot (F_{fil} + F_K) + \frac{F_K}{V_{ART}} \cdot P_{ART} + \frac{P_{intra,K}}{V_{intra,K}} \cdot (F_{fil} - F_{ex}) + \lambda_{phy} \cdot P_{K,v}^*
\]

\[
\frac{d}{dt} P_{K,v}^* = -\frac{P_{K,v}^*}{V_{K,v}} \cdot (F_{fil} + F_K) + \frac{F_K}{V_{ART}} \cdot P_{ART}^* + \frac{P_{intra,K}^*}{V_{intra,K}} \cdot (F_{fil} - F_{ex}) - \lambda_{phy} \cdot P_{K,v}^*
\]

Veins

\[
\frac{d}{dt} P_{VEN} = -k_{Pr} \cdot P_{VEN} + \sum_i \frac{F_i}{V_i} P_{i,v} - \frac{F_M}{V_M} P_{M,v} - \frac{F_{GI}}{V_{GI}} P_{Gl,v} + \frac{F_M + F_{GI}}{V_L} P_{L,v} + \lambda_{phy} \cdot P_{VEN}^*
\]

\[
\frac{d}{dt} P_{VEN}^* = -k_{Pr} \cdot P_{VEN}^* + \sum_i \frac{F_i}{V_i} P_{i,v}^* - \frac{F_M}{V_M} P_{M,v}^* - \frac{F_{GI}}{V_{GI}} P_{Gl,v}^* + \frac{F_M + F_{GI}}{V_L} P_{L,v}^* - \lambda_{phy} \cdot P_{VEN}^*
\]

Arteries

\[
\frac{d}{dt} P_{ART} = -\sum_i \frac{F_i}{V_{ART}} \cdot P_{i,v} + \frac{F}{V_{LU,v}} \cdot P_{LU,v} + \lambda_{phy} \cdot P_{ART}^*
\]

\[
\frac{d}{dt} P_{ART}^* = -\sum_i \frac{F_i}{V_{ART}} \cdot P_{i,v}^* + \frac{F}{V_{LU,v}} \cdot P_{LU,v}^* - \lambda_{phy} \cdot P_{ART}^*
\]

Free peptide, interstitial spaces:

Kidneys:

\[
\frac{d}{dt} P_{K,int} = -k_{on} \cdot P_{K,int} \cdot \frac{R_K}{V_{K,int}} + k_{off} \cdot RP_K + F_{fil} \left( \frac{P_{K,v}}{V_{K,v}} - \frac{P_{K,int}}{V_{K,int}} \right) + \lambda_{phy} \cdot P_{K,int}^*
\]

\[
\frac{d}{dt} P_{K,int}^* = -k_{on} \cdot P_{K,int}^* \cdot \frac{R_K}{V_{K,int}} + k_{off} \cdot RP_K^* + F_{fil} \left( \frac{P_{K,v}^*}{V_{K,v}} - \frac{P_{K,int}^*}{V_{K,int}} \right) - \lambda_{phy} \cdot P_{K,int}^*
\]
Muscle, red marrow, skin, lungs, adipose tissue, heart, bone, rest and brain \((PS = 0)\):

\[
\frac{d}{dt} P_{i, \text{int}} = PS_i \left( \frac{P_{i, \text{int}}^{*}}{V_{i, \text{int}}} - \frac{P_{i, \text{int}}}{V_{i, \text{int}}} \right) + \lambda_{\text{phy}} \cdot P_{i, \text{int}}^*
\]

\[
\frac{d}{dt} P_{i, \text{int}}^* = PS_i \left( \frac{P_{i, \text{int}}^{*}}{V_{i, \text{int}}} - \frac{P_{i, \text{int}}}{V_{i, \text{int}}} \right) - \lambda_{\text{phy}} \cdot P_{i, \text{int}}^*
\]

Parotid, submandibular and lacrimal glands, tumour, kidneys, liver, spleen, GI and prostate:

\[
\frac{d}{dt} P_{i, \text{int}} = -k_{\text{on}} \cdot P_{i, \text{int}} \cdot \frac{R_j}{V_{i, \text{int}}} + k_{\text{off}} \cdot R P_i + PS_i \left( \frac{P_{i, \text{int}}^{*}}{V_{i, \text{int}}} - \frac{P_{i, \text{int}}}{V_{i, \text{int}}} \right) + \lambda_{\text{phy}} \cdot P_{i, \text{int}}^*
\]

\[
\frac{d}{dt} P_{i, \text{int}}^* = -k_{\text{on}} \cdot P_{i, \text{int}}^* \cdot \frac{R_j}{V_{i, \text{int}}} + k_{\text{off}} \cdot R P_i^* + PS_i \left( \frac{P_{i, \text{int}}^{*}}{V_{i, \text{int}}} - \frac{P_{i, \text{int}}}{V_{i, \text{int}}} \right) - \lambda_{\text{phy}} \cdot P_{i, \text{int}}^*
\]

**Further equations:**

Peptide in kidney cells (unspecific)

\[
\frac{d}{dt} P_{\text{intra,K}} = \frac{P_{\text{intra,K}}^{\text{int}}}{V_{\text{intra,K}}} \cdot (F_{\text{fil}} - F_{\text{ex}}) - \frac{P_{\text{intra,K}}^{\text{int}}}{V_{\text{intra,K}}} \cdot (F_{\text{fil}} - F_{\text{ex}}) + \lambda_{\text{phy}} \cdot P_{\text{intra,K}}^*
\]

\[
\frac{d}{dt} P_{\text{intra,K}}^* = \frac{P_{\text{intra,K}}^{\text{int}}}{V_{\text{intra,K}}} \cdot (F_{\text{fil}} - F_{\text{ex}}) - \frac{P_{\text{intra,K}}^{\text{int}}}{V_{\text{intra,K}}} \cdot (F_{\text{fil}} - F_{\text{ex}}) - \lambda_{\text{phy}} \cdot P_{\text{intra,K}}^*
\]

Bound to protein

\[
\frac{d}{dt} PRP = k_{PR} \cdot P_{VEN} + \lambda_{\text{phy}} \cdot PRP^*
\]

\[
\frac{d}{dt} PRP^* = k_{PR} \cdot P_{VEN}^* - \lambda_{\text{phy}} \cdot PRP^*
\]
### TABLE A.1 Parameter definition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{on}$</td>
<td>association rate</td>
<td>0.046</td>
<td>nmol·l$^{-1}$·min$^{-1}$ (2)$^a$</td>
</tr>
<tr>
<td>$K_D$</td>
<td>dissociation constant</td>
<td>1</td>
<td>nmol$^{-1}$</td>
</tr>
<tr>
<td>$k_{off}$</td>
<td>dissociation rate</td>
<td>$K_D$·$k_{on}$</td>
<td>min$^{-1}$</td>
</tr>
<tr>
<td>$\lambda_{phy}$</td>
<td>physical decay $^{177}$Lu and $^{68}$Ga</td>
<td>7.15·10$^{-5}$/1.03·10$^{-2}$</td>
<td>min$^{-1}$</td>
</tr>
<tr>
<td>$BW$</td>
<td>body weight</td>
<td>measured</td>
<td>kg</td>
</tr>
<tr>
<td>$BH$</td>
<td>body height</td>
<td>measured</td>
<td>cm</td>
</tr>
<tr>
<td>$H$</td>
<td>hematocrit</td>
<td>measured</td>
<td>unity</td>
</tr>
<tr>
<td>$F$</td>
<td>flow total serum without tumour</td>
<td>$V_T$·1.23/min$^b$</td>
<td>1·min$^{-1}$ (3)</td>
</tr>
<tr>
<td>$V_T$</td>
<td>volume of total body serum</td>
<td>2.8·(1-$H$)·BSA·(l·m$^{-2}$)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>$BSA$</td>
<td>body surface area</td>
<td>0.007184·$BF^{0.725}$·$BW^{0.425}$</td>
<td>m$^2$ (4)</td>
</tr>
<tr>
<td>$\rho$</td>
<td>assumed density for all organs and tumour</td>
<td>1 ml ± 1 g</td>
<td></td>
</tr>
</tbody>
</table>

#### Tumour

| $V_{TU,total}$            | total volume of tumour 1 and 2             | $V_{TU,total,0}$·$e^{V_{TU,total,1}$·[TU-BED(\)]} | 1 |
| $V_{TU,total,0}$          | total volume of tumour 1 and 2 at time of PET/CT | measured | 1 |
| $\Delta T$                | Elapsed time after first PET/CT            | measured | min |
| $BED_{TU}$                | Biologically effective dose tumour         | equation 2 manuscript | Gy$^{-1}$ |
| $\alpha_{TU}$             | Radiosensitivity of tumour cells           | fitted | Gy$^{-1}$ |
| $\lambda_g$               | growth rate for androgen independent tumour cells | bone: 5.12·10$^{-6}$ | min$^{-1}$ (5) |
| $V_{TU,Rest,total}$       | total volume of rest tumour time of therapy | $x_V$·$V_{TU,Rest,vol}$·$e^{V_{TU,Rest,vol}$·[TU-BED(\)]} | 1 |
| $V_{TU,Rest,total,0}$     | total volume of rest tumour time of PET     | $x_V$·$V_{TU,Rest,vol}$ | 1 |
| $V_{VOL,TU,Rest}$         | PET/CT volume with 15-20% SUV max          | measured | 1 |
| $\chi_V$                  | ratio between actual volume and PET/CT volume | Ratio derived from lesion 1 and 2 | unity |
| $V_{TU,int}$              | interstitial space of tumour               | $V_{TU,int}$ | 1 |
| $V_{TU, v}$               | vascular space of tumour                   | $V_{TU,v}$ | 1 |
| $V_{TU,Rest, int}$        | interstitial space of tumour remainder     | $V_{TU,Rest,int}$ | 1 |
| $V_{TU, Rest, v}$         | vascular space of tumour remainder         | $V_{TU, Rest, v}$ | 1 |
| $V_{TU, int}$             | interstitial space fraction of total tumour | 0.38 | unity (6) |
| $V_{TU,V}$                | vascular (serum) fraction of total tumour  | 0.05·(1-$H$) | unity (7) |
| $f_{TU}$                  | serum flow tumour                          | $f_{TU}$ | 1·min$^{-1}$ |
| $f_{TU, Rest}$            | serum flow tumour remainder                | $f_{TU}$ | 1·min$^{-1}$ |
| $f_{TU, int}$             | serum flow density tumour                  | fitted | ml·min$^{-1}$·g$^{-1}$ (7,8) |
| $f_{TU, Rest}$            | serum flow density tumour                  | fitted | ml·min$^{-1}$·g$^{-1}$ |
| $PS_{TU}$                 | permeability surface area product tumour   | $k_{TU}$ | ml·min$^{-1}$ |
| $PS_{TU, Rest}$           | permeability surface area product remainder | $k_{TU}$ | ml·min$^{-1}$ |
| $k_{TU}$                  | permeability surface area product tumour per unit mass (scaled for molecule size of PSMA I&T) | 0.6 (maximal value from (6)) | ml·min$^{-1}$·g$^{-1}$ |
| $k_{TU, Rest}$            | permeability surface area product tumour per unit mass (scaled for molecule size of PSMA I&T) | $k_{TU, Rest}$ | ml·min$^{-1}$·g$^{-1}$ |
| $[RU,O]$                  | PSMA receptor density                      | fitted | nmol·F$^{-1}$ |
| $[RU,Rest, 0]$            | PSMA receptor density tumour remainder     | $x_V$·$([RU,Rest, 0]$·$V_{TU, Rest,0}$+ $[RU,Rest, 0]$·$V_{TU, Rest,0}$) | nmol·F$^{-1}$ |
| $x_V$                     | ratio between actual and assumed receptor density of tumour remainder | 1 | unity |
| $RU,O$                    | PSMA receptor number                       | $[RU,O]$ | nmol |
| $RU,Rest, 0$              | PSMA receptor number tumour remainder      | $[RU,Rest, 0]$ | nmol |
| $\lambda_{TU,int}$        | internalisation rate tumour                | 0.001 | min$^{-1}$ (10) |

---

$^a$ Source: TU Muenchen on July 24, 2018. For personal use only.
\begin{table}
\centering
\begin{tabular}{llll}
\hline
\(\dot{\lambda}_{\text{TU,release}}\) & release rate tumour & fitted & min\(^{-1}\) \\
\(\dot{\lambda}_{\text{TU,Rest,int}}\) & internalisation rate tumour remainder & 0.001 & min\(^{-1}\) (10) \\
\(\dot{\lambda}_{\text{TU,Rest,release}}\) & release rate tumour remainder & \((\dot{\lambda}_{\text{TU,1,release}} + \dot{\lambda}_{\text{TU,2,release}})/2\) & min\(^{-1}\) \\
\hline
\end{tabular}

\textbf{Liver, spleen and kidneys}

\begin{tabular}{llll}
\hline
\(V_{\text{L,total}}\) & volume total liver & CT measured & 1 (11) \\
\(V_{\text{S,total}}\) & volume total spleen & CT measured & 1 \\
\(V_{\text{K,total}}\) & volume total kidneys & CT measured & 1 \\
\(V_{\text{LV}}\) & vascular (serum) volume organ liver, spleen, kidneys & \(V_{\text{L,total}}\cdot V_{\text{LV}}\) & 1 \\
\(V_{\text{int}}\) & interstitial volume liver, spleen, kidneys & \(V_{\text{L,total}}\cdot V_{\text{int}}\) & 1 \\
\(V_{\text{K, intra}}\) & volume intracellular kidneys & \((V_{\text{K,total}} - V_{\text{K,int}} - V_{\text{K,spl}})\cdot 2/3\) & 1 \\
\(V_{\text{LV}}\) & vascular (serum) fraction liver & 0.085 & unity (12) \\
\(V_{\text{SV}}\) & vascular (serum) fraction spleen & 0.12 & unity (12) \\
\(V_{\text{VK}}\) & vascular (serum) fraction kidneys & 0.055 & unity (12) \\
\(V_{\text{int}}\) & interstitial fraction liver & 0.2 & unity (12) \\
\(V_{\text{int}}\) & interstitial fraction spleen & 0.2 & unity (12) \\
\(V_{\text{int}}\) & interstitial fraction kidneys & 0.15 & unity (12) \\
\(F_{\text{L}}\) & serum flow liver arterial & 0.065·\(F\) & l·min\(^{-1}\) (3) \\
\(F_{\text{s}}\) & serum flow spleen & 0.03·\(F\) & l·min\(^{-1}\) (3) \\
\(F_{\text{k}}\) & serum flow kidney & \(F_{\text{k},0}\cdot F_{\text{k}}\cdot (1-H)\) & l·min\(^{-1}\) \\
\(f_{\text{k}}\) & age dependent blood flow to the kidney & \(f_{\text{k},0} = 0.026\) Age & ml·min\(^{-1}\)·g\(^{-1}\) (13) \\
\(f_{\text{k},0}\) & kidney blood flow, age independent factor for all ages & fitted & ml·min\(^{-1}\)·g\(^{-1}\) \\
\(\phi_{\text{therapy}}\) & ratio of sieving coefficients therapy & \(\phi_{\text{PSMA,IKT}} / \phi_{\text{C,51,EDTA}} = 0.66\) & unity (14) \\
\(\phi_{\text{PET}}\) & ratio of sieving coefficients PET/CT & \(\phi_{\text{PET}} / \phi_{\text{C,51,EDTA}} = 0.75\) & unity \\
\(GFR\) & glomerular filtration rate with \(^{31}\text{Cr}-\text{EDTA}\) & \(F_{\text{k},0}\cdot x_{k}\) & l·min\(^{-1}\) (15) \\
\(x_{k}\) & filtered fraction of blood blow & fitted & unity \\
\(F_{\text{fil}}\) & filtration & \(F_{\text{fil}}/f_{\text{ex}}\) & l·min\(^{-1}\) \\
\(F_{\text{ex}}\) & excretion & fitted & unity \\
\(f_{\text{ex}}\) & excretion fraction & 0.96 & unity (16) \\
\(k_{\text{L}}\) & permeability surface area product per unit mass for liver & \(k_{\text{MUS}}\cdot 100\) & ml·min\(^{-1}\)·g\(^{-1}\) (17) \\
\(k_{\text{S}}\) & permeability surface area product per unit mass for spleen & \(k_{\text{L}}\) (due to similar capillary structure) & ml·min\(^{-1}\)·g\(^{-1}\) \\
\(R_{\text{L,0}}\) & receptor density liver & \([R_{\text{PRO,0}}] = 0.05\) & nmol·l\(^{-1}\) (18) \\
\(R_{\text{S,0}}\) & receptor density spleen & \([R_{\text{K,0}}] = 0.2\) & nmol·l\(^{-1}\) (18) \\
\(R_{\text{K,0}}\) & receptor density kidneys & fitted & nmol·l\(^{-1}\) \\
\(\lambda_{\text{L, int}}\) & internalization rate PSMA liver & \(\lambda_{\text{TU, int}}\) & min\(^{-1}\) (19) \\
\(\lambda_{\text{S, int}}\) & internalization rate PSMA spleen & \(\lambda_{\text{TU, int}}\) & min\(^{-1}\) (19) \\
\(\lambda_{\text{K, int}}\) & internalization rate PSMA kidneys & \(\lambda_{\text{TU, int}}\) & min\(^{-1}\) (19) \\
\(\lambda_{\text{L,release}}\) & release rate liver & \(\lambda_{\text{TU, release}}\) & min\(^{-1}\) (16,20) \\
\(\lambda_{\text{S,release}}\) & release rate spleen & \(\lambda_{\text{TU, release}}\) & min\(^{-1}\) (16) \\
\(\lambda_{\text{K,release}}\) & release rate kidneys & fitted & min\(^{-1}\) \\
\hline
\end{tabular}

\textbf{Other organs}

\begin{tabular}{llll}
\hline
\(V_{\text{PRO,total}}\) & volume total prostate (not removed for patients with 
prostatectomy) & 0.016·\(BW/71\) & 1 (21) \\
\(V_{\text{L,LU,total}}\) & volume total lungs & 1·\(BW/71\) & 1 (21) \\
\(V_{\text{S,PA,total}}\) & volume total parotid gland & CT measured & 1 \\
\(V_{\text{S,LAC,tot}}\) & volume total lacrimal glands & CT measured & 1 \\
\(V_{\text{S,MUS,tot}}\) & volume total submandibular glands & CT measured & 1 \\
\(V_{\text{MUS,tot}}\) & volume total muscles & 30.078·\(BW/71\) & 1 (21) \\
\(V_{\text{GI,tot}}\) & volume total GI + pancreas & (0.385+0.548+0.104+0.15)·\(BW/71\) & 1 (21) \\
\hline
\end{tabular}
\end{table}
\[ \begin{array}{|c|c|c|}
\hline
V_{\text{SKIN, total}} & \text{volume total skin} & 3.408 \cdot BW/71 \\
V_{\text{ADI, total}} & \text{volume total adipose tissue} & 13.465 \cdot BW/71 \\
V_{\text{RM, total}} & \text{volume total red marrow} & 1.1 \cdot BW/71 \\
V_{\text{BONE, total}} & \text{volume total bone without red marrow} & 10.165 \cdot BW/71 - V_{\text{RM, total}} \\
V_{\text{HRT, total}} & \text{volume total heart} & 0.341 \cdot BW/71 \\
V_{\text{BR, total}} & \text{volume total brain} & 1.45 \cdot BW/71 \\
V_{\text{BW}} & \text{volume of total body based on BW} & 1 \text{ ml } \Delta \text{ 1 g} \\
\hline
V_{\text{REST, total}} & \text{volume of rest body} & V_{\text{BW}} - \sum_{i} V_{i, \text{total}} \\
V_{\text{PRO, v}} & \text{vascular volume prostate} & 0.004 \cdot (1 - H) V_{\text{PRO, total}} \\
V_{\text{LU, v}} & \text{vascular (serum) volume lungs} & 0.105 \cdot V_{\text{P}} \\
V_{\text{SAL, v}} & \text{vascular (serum) volume parotid glands} & 0.03 \cdot (1 - H) V_{\text{SAL, total}} \\
V_{\text{LAC, v}} & \text{vascular (serum) volume lacrimal glands} & 0.03 \cdot (1 - H) V_{\text{LAC, total}} \\
V_{\text{SUB, v}} & \text{vascular (serum) volume submandibular glands} & 0.03 \cdot (1 - H) V_{\text{SUB, total}} \\
V_{\text{MUS, v}} & \text{vascular (serum) volume muscles} & 0.14 \cdot V_{\text{P}} \\
V_{\text{GL, v}} & \text{vascular (serum) volume GI + pancreas} & 0.076 \cdot V_{\text{P}} \\
V_{\text{SKIN, v}} & \text{vascular (serum) volume skin} & 0.03 \cdot V_{\text{P}} \\
V_{\text{ADI, v}} & \text{vascular (serum) volume adipose tissue} & 0.05 \cdot V_{\text{P}} \\
V_{\text{RM, v}} & \text{vascular (serum) volume red marrow} & 0.04 \cdot V_{\text{P}} \\
V_{\text{BONE, v}} & \text{vascular (serum) volume bone without red marrow} & 0.07 \cdot V_{\text{P}} - V_{\text{RM, v}} \\
V_{\text{HRT, v}} & \text{vascular (serum) volume heart (supply)} & 0.01 \cdot V_{\text{P}} \\
V_{\text{BR, v}} & \text{vascular (serum) volume brain} & 0.012 \cdot V_{\text{P}} \\
\hline
V_{\text{REST, v}} & \text{serum volume rest}\ i = \text{all organs except tumour} & V_{\text{P}} - \sum_{i} V_{i, \text{v}} \\
V_{\text{ART}} & \text{arterial serum plus} \ 1/2 \text{ serum content of heart} & 0.06 \cdot V_{\text{P}} + 0.045 \cdot V_{\text{P}} \\
V_{\text{VEN}} & \text{venous serum plus} \ 1/2 \text{ serum content of heart} & 0.18 \cdot V_{\text{P}} + 0.045 \cdot V_{\text{P}} \\
V_{\text{PRO, int}} & \text{interstitial fraction prostate} & 0.25 \cdot V_{\text{PRO, total}} \\
V_{\text{LU, int}} & \text{interstitial fraction lungs} & V_{\text{LU, v}} \cdot \alpha_{\text{LU}} \\
V_{\text{SAL, int}} & \text{interstitial fraction parotid glands} & 0.23 \cdot V_{\text{SAL, total}} \\
V_{\text{LAC, int}} & \text{interstitial fraction lacrimal glands} & 0.23 \cdot V_{\text{LAC, total}} \\
V_{\text{SUB, int}} & \text{interstitial fraction submandibular glands} & 0.23 \cdot V_{\text{SUB, total}} \\
V_{\text{MUS, int}} & \text{interstitial fraction muscles} & V_{\text{MUS, v}} \cdot \alpha_{\text{MUS}} \\
V_{\text{GL, int}} & \text{interstitial fraction GI + pancreas} & V_{\text{GL, v}} \cdot \alpha_{\text{GL}} \\
V_{\text{SKIN, int}} & \text{interstitial fraction skin} & V_{\text{SKIN, v}} \cdot \alpha_{\text{SKIN}} \\
V_{\text{ADI, int}} & \text{interstitial fraction adipose tissue} & V_{\text{ADI, v}} \cdot \alpha_{\text{ADI}} \\
V_{\text{RM, int}} & \text{interstitial fraction red marrow} & V_{\text{RM, v}} \cdot \alpha_{\text{RM}} \\
V_{\text{BONE, int}} & \text{interstitial fraction bone without red marrow} & V_{\text{BONE, v}} \cdot \alpha_{\text{BONE}} \\
V_{\text{HRT, int}} & \text{interstitial fraction heart} & V_{\text{HRT, v}} \cdot \alpha_{\text{HRT}} \\
V_{\text{REST, v}} & \text{volume of rest body} & V_{\text{REST, v}} \cdot \alpha_{\text{REST}} \\
\hline
\alpha_{\text{MUS}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{MUS, int}}/V_{\text{MUS, v}} = 5.9 & \text{unity} \\
\alpha_{\text{GL}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{GL, int}}/V_{\text{GL, v}} = 8.8 & \text{unity} \\
\alpha_{\text{SKIN}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{SKIN, int}}/V_{\text{SKIN, v}} = 8.9 & \text{unity} \\
\alpha_{\text{ADI}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{ADI, int}}/V_{\text{ADI, v}} = 15.5 & \text{unity} \\
\alpha_{\text{RM}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{RM, int}}/V_{\text{RM, v}} = 3.7 & \text{unity} \\
\alpha_{\text{HRT}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{HRT, int}}/V_{\text{HRT, v}} = 3.7 & \text{unity} \\
\alpha_{\text{LU}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{LU, int}}/V_{\text{LU, v}} = 5.5 & \text{unity} \\
\alpha_{\text{BONE}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{BONE, int}}/V_{\text{BONE, v}} = 8.4 & \text{unity} \\
\alpha_{\text{REST}} & \text{ratio of interstitial to vascular volume average man} & V_{\text{REST, int}}/V_{\text{REST, v}} = 4.1 & \text{unity} \\
\hline
f_{\text{PRO}} & \text{serum flow density prostate} & 0.18 \cdot (1 - H) & \text{ml min}^{-1} \cdot \text{g}^{-1} \\
f_{\text{PRO}} & \text{total serum flow to prostate} & f_{\text{PRO}} \cdot V_{\text{PRO, total}} & \text{ml min}^{-1} \\
f_{\text{SAL}} & \text{serum flow density parotid glands} & 0.16 & \text{ml min}^{-1} \cdot \text{g}^{-1} \\
F_{\text{SAL}} & \text{total serum flow to parotid glands} & f_{\text{SAL}} \cdot V_{\text{SAL, total}} & \text{ml min}^{-1} \\
\hline
\end{array} \]
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_{\text{LAC}} )</td>
<td>serum flow density lacrimal glands</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{LAC}} )</td>
<td>total serum flow to lacrimal glands</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( f_{\text{SAL}} )</td>
<td>serum flow density submandibular glands</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{SAL}} )</td>
<td>total serum flow to submandibular glands</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( f_{\text{SUB}} )</td>
<td>serum flow density submandibular glands</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{SUB}} )</td>
<td>total serum flow to submandibular glands</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{LU}} )</td>
<td>total serum flow lungs</td>
<td>ml·min(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{MUS}} )</td>
<td>total serum flow to muscle</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{GI}} )</td>
<td>total serum flow to GI+ pancreas</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{SKIN}} )</td>
<td>total serum flow to skin</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{ADI}} )</td>
<td>total serum flow to adipose</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{RM}} )</td>
<td>total serum flow to red marrow (RM)</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{BONE}} )</td>
<td>total serum flow to bone</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{HRT}} )</td>
<td>total serum flow to heart</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{BR}} )</td>
<td>total serum flow to brain</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( F_{\text{REST}} )</td>
<td>total serum flow to rest</td>
<td>ml·min(^{-1})·g(^{-1})</td>
</tr>
</tbody>
</table>

\[ F_{\text{REST}} = \sum_{i} F_{i} \]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( F_{\text{TOTAL}} )</td>
<td>total serum flow including tumour tissue</td>
<td>ml·min(^{-1})</td>
</tr>
<tr>
<td>( V_{i} )</td>
<td>permeability surface area product</td>
<td>( k_{i} V_{i,\text{total}} ) ml·min(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{PRO}} )</td>
<td>permeability surface area product per unit mass (scaled for molecule size of PSMA I&amp;T) for prostate</td>
<td>0.1 ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{LU}} )</td>
<td>permeability surface area product per unit mass for lungs</td>
<td>( k_{\text{MUS}} \cdot 100 ) ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{SAL}} )</td>
<td>permeability surface area product per unit mass for parotid glands</td>
<td>0.4 ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{LAC}} )</td>
<td>permeability surface area product per unit mass for lacrimal glands</td>
<td>( k_{\text{SAL}} ) ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{SUB}} )</td>
<td>permeability surface area product per unit mass for submandibular glands</td>
<td>( k_{\text{SAL}} ) ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{MUS}} )</td>
<td>permeability surface area product per unit mass for muscle</td>
<td>0.02 ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{GI}} )</td>
<td>permeability surface area product per unit mass for GI and pancreas</td>
<td>0.02 ml·min(^{-1})·g(^{-1}) (assumed to similar to muscle)</td>
</tr>
<tr>
<td>( k_{\text{SKIN}} )</td>
<td>permeability surface area product per unit mass for skin</td>
<td>0.02 ml·min(^{-1})·g(^{-1}) (assumed to similar to muscle)</td>
</tr>
<tr>
<td>( k_{\text{ADI}} )</td>
<td>permeability surface area product per unit mass for adipose</td>
<td>0.02 ml·min(^{-1})·g(^{-1}) (assumed to similar to muscle)</td>
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<tr>
<td>( k_{\text{RM}} )</td>
<td>permeability surface area product per unit mass for red marrow</td>
<td>( k_{L} ) (assumed to similar to liver) ml·min(^{-1})·g(^{-1})</td>
</tr>
<tr>
<td>( k_{\text{HRT}} )</td>
<td>permeability surface area product per unit mass for heart</td>
<td>0.02 ml·min(^{-1})·g(^{-1}) (assumed to similar to muscle)</td>
</tr>
<tr>
<td>( k_{\text{BONE}} )</td>
<td>permeability surface area product per unit mass for bone</td>
<td>0.02 ml·min(^{-1})·g(^{-1}) (assumed to similar to muscle)</td>
</tr>
<tr>
<td>( k_{\text{REST}} )</td>
<td>permeability surface area product per unit mass for rest</td>
<td>0.02 ml·min(^{-1})·g(^{-1}) (assumed to similar to muscle)</td>
</tr>
</tbody>
</table>
\[R_{\text{PRO},0}\] receptor density prostate \[R_{\text{TU,Res},0}\] \cdot 110 \text{ nmol l}^{-1} (23,25)

\[R_{\text{SAL},0}\] receptor density parotid glands 42 \text{ nmol l}^{-1} (23)

\[R_{\text{LAC},0}\] receptor density lacrimal glands \[R_{\text{SAL},0}\] \text{ nmol l}^{-1}

\[R_{\text{SUB},0}\] receptor density submandibular glands \[R_{\text{SAL},0}\] \text{ nmol l}^{-1}

\[R_{\text{GLO},0}\] receptor density GI + pancreas \[R_{\text{PRO},0}\] \cdot 0.06 \text{ nmol l}^{-1} (18)

\[\lambda_{\text{NT,int}}\] internalization rate for normal tissue \[\lambda_{\text{TU,int}}\] \text{ min}^{-1} (19)

\[\lambda_{\text{SAL,release}}\] degradation and release parotid glands 0.00037 \text{ min}^{-1} (23)

\[\lambda_{\text{LAC,release}}\] degradation and release lacrimal glands \[\lambda_{\text{SAL,release}}\] \text{ min}^{-1}

\[\lambda_{\text{SUB,release}}\] degradation and release submandibular glands \[\lambda_{\text{SAL,release}}\] \text{ min}^{-1}

\[\lambda_{\text{NT,release}}\] degradation and release normal tissue except salivary glands \[\lambda_{\text{K,release}}\] \text{ min}^{-1}

\[R_{i,0}\] receptors total number of PSMA positive organ \[R_{i,0}\] \cdot V_{\text{total}} \text{ nmol}

\[R_{i,0}\] receptor density of PSMA positive organ \[R_{i,0}\] \text{ nmol l}^{-1}

\[R_{p}\] peptide bound \text{ nmol}

\[P_{\text{PRP}}\] peptide bound to serum protein \text{ nmol}

\[k_{\text{PR}}\] binding rate peptide to serum 4.7 \cdot 10^{-4} \text{ min}^{-1} (10)

\[P_{\text{int,1}}\] peptide internalized \text{ nmol}

\[P_{\text{int,2}}\] peptide free vascular \text{ nmol}

\[P_{\text{int,3}}\] peptide free interstitial \text{ nmol}

\[P_{K,\text{intra}}\] peptide intracellular kidneys \text{ nmol}

\[P_{\text{inj}}\] injected amount of unlabeled peptide P1-5: 139; 91; 81; 67; 294 \text{ nmol}

\[P_{*\text{inj}}\] injected amount of labeled peptide P1-5: 8.4; 7.5; 7.5; 7.5; 7.8 \text{ nmol}

\(a\) Mean values from all measured (surface-plasmon-resonance-spectroscopy) ligands. The measured dissociation constant values are considerably lower than reported in the literature. The values for the therapeutic (26) and PET ligand (27) are very similar. Using the \(K_D\) literature values (26,27), which were derived using competitive cell binding (\(K_D =12\) nM) or enzyme based assays (\(K_D =7.5\) nM), for fitting the PBPK/PD model to human data, leads to inferior results (e.g. lower \(R^2\) and higher AICc). Thus, it seems that \(k_{\text{on}}\) and \(k_{\text{off}}\) values determined using surface-plasmon-resonance-spectroscopy are more supported by human in vivo data.

\(b\) For the average normal adult (blood) \(F = 6500\) ml/min and \(V = 5300\) ml. Therefore, a factor of 1.23 was assigned to account for the changes in total serum flow due to volume changes.

\(c\) Using the assumption of 266 nmol\(\text{l}^{-1}\) receptor density (9), \(10^{12}\) cells per liter and 10 ml or 50 ml addition tumour volume.
It is assumed that 2/3 of the total intracellular volume of the kidneys is represented by the proximal tubular cells.

Scaling of GFR due to different molecular sizes.
Absorbed dose ($D$) and biologically effective dose ($BED$):

To calculate the absorbed dose (only self-dose was considered) and the $BED$ of the kidneys and tumour the following equations and parameter values (Table B) were used:

\[
\dot{D}_i(t) = A_i(t) \cdot S_{i\tau-i} = A_{inj} \cdot a_i(t) \cdot S_{i\tau-i}
\]  \hspace{1cm} (14)

\[
D_i(T) = \int_0^T \dot{D}_i(t) \, dt = A_{inj} \cdot \tilde{a}_i(T) \cdot S_{i\tau-i}
\]  \hspace{1cm} (15)

The $BED$ (28) is defined as

\[
BED_i = D_i \cdot (1 + \frac{G_i}{\alpha_i / \beta_i})
\]  \hspace{1cm} (16)

The factor $G_i$ (Lea–Catcheside factor) (28) is defined as

\[
G_i(T) = \frac{2}{D_i^2} \cdot \int_0^T \dot{D}_i(t) \, dt \cdot \int_0^\omega \dot{D}_i(\omega) \cdot e^{-\mu_{(\tau-\omega)}} \, d\omega
\]  \hspace{1cm} (17)

Thus, after inserting Eq. (17) in (16) one obtains

\[
BED_i = D_i + \frac{2 \cdot \int_0^T \dot{D}_i(t) \, dt \cdot \int_0^\omega \dot{D}_i(\omega) \cdot e^{-\mu_{(\tau-\omega)}} \, d\omega}{\alpha_i / \beta_i}
\]  \hspace{1cm} (18)
### Table A.2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
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<tbody>
<tr>
<td>$S_{K\leftarrow K}$</td>
<td>Dose factor kidneys to kidneys</td>
<td>$4.82 \cdot 10^{-6} \cdot 0.299 / V_{K,\text{total,measured}}$</td>
<td>(11)</td>
</tr>
<tr>
<td>$S_{TU\leftarrow TU}$</td>
<td>Dose factor tumour to tumour $^a$</td>
<td>$S = 82.81 / (V_{TU,\text{total}} \cdot 1000) + 1.21 / (V_{TU,\text{total}} \cdot 1000)^{2/3} - 0.11 / (V_{TU,\text{total}} \cdot 1000)^{1/3}$</td>
<td>Gy·min$^{-1}$·MBq$^{-1}$</td>
</tr>
<tr>
<td>$\alpha/\beta_K$</td>
<td>radiobiological parameters kidneys</td>
<td>2.5</td>
<td>Gy</td>
</tr>
<tr>
<td>$\mu_K$</td>
<td>repair rate kidneys</td>
<td>ln(2)/60/2.8</td>
<td>min$^{-1}$</td>
</tr>
<tr>
<td>$\alpha/\beta_{TU}$</td>
<td>radiobiological parameters tumour</td>
<td>1.49</td>
<td>Gy</td>
</tr>
<tr>
<td>$\mu_{TU}$</td>
<td>repair rate tumour</td>
<td>ln(2)/60/1.9</td>
<td>min$^{-1}$</td>
</tr>
<tr>
<td>$\tilde{a}_i$</td>
<td>time-integrated activity coefficient of organ $i$</td>
<td></td>
<td>h</td>
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<tr>
<td>$a_i$</td>
<td>fraction of administered activity of organ $i$</td>
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<td>unity</td>
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<tr>
<td>$D_i$</td>
<td>dose to organ $i$</td>
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<td>Gy</td>
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<td>$D_{Ti}$</td>
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<tr>
<td>$T$</td>
<td>Integration time</td>
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<td>$G_i$</td>
<td>Lea–Catcheside factor of organ $i$</td>
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<tr>
<td>$BED_i$</td>
<td>biologically effective dose to organ $i$</td>
<td></td>
<td>Gy</td>
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</table>

$^a$The function $S = A / (V_{TU,\text{total}} \cdot 1000) + B / (V_{TU,\text{total}} \cdot 1000)^{2/3} - C / (V_{TU,\text{total}} \cdot 1000)^{1/3}$ (valid for tumours > 1 ml) was fitted to the OLINDA data for $^{177}$Lu spheres.
References


PBPK Model compartments

Figure A. Main model structure: All organs are represented by a rectangular compartment and connected via the serum flow. Each organ within this model, except arteries, veins, brain and protein serum, is divided into sub-compartments. The substance is cleared via the kidneys. The compartment “Peptide-Protein serum” contains peptide bound to serum protein. As the fraction of bound peptide to proteins is small compared to the total amount and to reduce complexity, only the „veins“ were connected to this compartment. The corresponding fraction for each specific organ is considered in the fitting process by assigning the data to the specific compartments.
**Figure B1. GI, spleen, prostate, submandibular, lacrimal and parotid glands and tumour:** The entire model consists of three systems, one for labelled (with *) and one for unlabelled peptide. The systems are connected by the competition for free receptors ($k_{on, non,i} = k_{on}(R_{0,i} - RP_i - RP_i^*)/V_{i,int}$) and by physical decay ($\lambda_{phys}$). All physiological parameters are assumed to be equal for the labelled and unlabelled substance.

$k_{off}$ is the dissociation rate, the transport of peptide via serum flow to organ $i$ is described by $F_i/V_{ART}$ (where $F_i$ is serum flow and $V_{ART}$ is serum volume of the arteries), $F_i/V_{i,v}$ describes the transport of peptide via serum flow out of organ and (where $F_i$ is serum flow and $V_{i,v}$ is serum volume of the respective organ, $RP_i$ is PSMA specific bound peptide to the cell surface, $P_{i,v}$ and $P_{i,int}$ free peptide of the vascular ($V_{i,v}$) and interstitial space ($V_{i,int}$), respectively. $PS_i$ is the permeability surface area product and $\lambda_{i,release}$ is the internalisation rate of bound peptide and $\lambda_{i,release}$ the release rate of $^{177}$Lu from the cell.
Figure B2. Liver: For the liver the model description of B1 applies but the serum flow is composed of liver arterial, GI and spleen flow.

Figure B3. Kidneys: The peptide is transported via serum flow to the vascular compartment then filtrated into the interstitial part. Due to the administration of amino acids the largest fraction ($f_{ex} = 0.96$) of peptide is excreted. All unspecific uptake mechanisms are modelled with flow $GFR \cdot \phi \cdot (1-f_{ex})$ in and out of kidney cells. $GFR$ was measured with Cr-51-EDTA.
Figure C. PSMA negative tissue and brain: For adipose, bone (other than red marrow), skin, heart (C1) and lung (C2) the model on the organ level simplifies to the transport of peptide via serum flow and transcapillary extravasation. For brain (C3) the model reduces to serum flow.
Figure D. Arteries and veins: As the fraction of bound peptide to proteins (PRP) is small compared to the total amount and to reduce complexity, only the „veins (D2)“ were connected to PRP. The corresponding fraction for each specific organ is considered in the fitting process by assigning the data to the specific compartments.
B. Background corrections

Assigning tumour data from planar scintigraphy to model compartments

For fitting the model parameters to the data derived from the therapeutic planar images, the following equation was used to assign the tumour data to the compartments of the PBPK model:

$$a_{TU, Therapy}(t) = \frac{P_{TU, v}(t) + P_{TU, int}(t) + RP_{TU}(t) + P_{TU, intern}(t)}{\text{amount injected, therapy}} \cdot \frac{(A_{ROILTU} \cdot h_{PET, TU})}{\text{amount injected, therapy} \cdot f_{hot}}$$ (B.1)

Where $a(t)$ is the fraction of administered activity of a specific tumour ROI, amount injected is the total injected therapy amount, $f_{hot}$ is the fraction of labelled peptide, $A_{ROILTU}$ is the area of the drawn ROI in the planar image, $h_{PET, TU}$ is the patient thickness (minus tumour diameter) at the particular location of the tumour measured in the PET/CT image, $V_{MUS, total}$ and $V_{ADI, total}$ is the total muscle and adipose volume (Supplement A) and $P_{TU, v}(t) + P_{TU, int}(t) + RP_{TU}(t) + P_{TU, intern}(t)$ are the amount of labelled peptide in the vascular, interstitial, bound and internalized tumour compartment, respectively. $P_{MUS, v}(t)$, $P_{MUS, int}(t)$, $P_{ADI, v}(t)$ and $P_{ADI, int}(t)$ describe the amount of labelled peptide in the vascular and interstitial spaces of muscle and adipose tissue, respectively. For tumour dose calculation only compartments pertaining to the tumour were used. The fraction of peptide bound to blood pool protein was neglected.

Assigning tumour data from PET/CT to model compartments
For fitting the model parameters to the data derived from the pre-therapeutic PET/CT images, the following equation was used to assign the data to the compartments of the PBPK model:

\[
\alpha_{\text{TU,PET}}(t) = \frac{P_{\text{TU},v}(t) + P_{\text{TU},\text{int},v}(t) + R_{\text{TU}}(t) + P_{\text{TU},\text{int},r}(t) + \frac{(V_{\text{VOI},2} - V_{\text{VOI},1})}{V_{\text{MU} \text{S},\text{total}} + V_{\text{ADL},\text{total}}}(P_{\text{MUS},v}(t) + P_{\text{MUS},\text{int},v}(t) + P_{\text{ADL},v}(t) + P_{\text{ADL},\text{int},v}(t))}{\text{amount injected}_{\text{PET}} / \text{hot}_{\text{PET}}}
\] (B.2)

Where \(V_{\text{VOI},1}\) is the estimated volume using the pre-therapeutic PET image with an threshold of 20-50% so that the CT tumour volume and the PET match. \(V_{\text{VOI},2}\) is the estimated volume using the pre-therapeutic PET image with an threshold of 10-20% leading to a 5 mm larger radius (i.e. one voxel) that for \(V_{\text{VOI},2}\) to get all activity contained in the tumour. The activity derived using \(V_{\text{VOI},2}\) was used as data point \(a_{\text{TU,PET}}(t)\) and was indirectly background corrected using the above described data assignment.

**Assigning REST tumour data from PET/CT to model compartments**

For tumour remainder (rest), the following equation was used in the fitting of model parameters to the data derived from the pre-therapeutic PET/CT images:

\[
\alpha_{\text{TU,Rest,PET}}(t) = \frac{P_{\text{TU},\text{Rest},v}(t) + P_{\text{TU},\text{Rest,\text{int}},v}(t) + R_{\text{TU},\text{Rest}}(t) + P_{\text{TU},\text{Rest,\text{int},r}}(t) + \frac{V_{\text{VOI},\text{Rest}}(1-x_v)}{V_{\text{MU} \text{S},\text{total}} + V_{\text{ADL},\text{total}}}(P_{\text{MUS},v}(t) + P_{\text{MUS},\text{int},v}(t) + P_{\text{ADL},v}(t) + P_{\text{ADL},\text{int},v}(t))}{\text{amount injected}_{\text{PET}} / \text{hot}_{\text{PET}}}
\] (B.3)

\(a_{\text{TU,Rest,PET}}(t)\) was derived with an threshold of 15-20%. Where \(x_v\) is the correction factor to get the actual tumour volume (this information is derived from two tumour lesions). \(x_v\) P1-13: 0.62, 0.55, 0.67, 0.55, 0.53, 0.58, 0.61, 0.72, 0.44, 0.34, 0.35, 0.62, 0.55.

**Assigning kidney data from PET/CT to model compartments**
\[
\begin{align*}
\alpha_{K,\text{PET}}(t) &= \frac{P_{K,v}(t)+P_{K,\text{int}}(t)+P_{K,\text{intern}}(t)+P_{K,v}(t)\cdot \frac{(V_{\text{VOL,k}}-V_{K,\text{total}})}{(V_{\text{MUS,\text{total}}}+V_{\text{ADI,\text{total}}})}}{\text{amount injected}_{\text{PET}}/f_{\text{hot,PET}}} \\
\end{align*}
\] (B.4)

Where \( V_{\text{VOL,k}} \) is the volume used for activity quantification with an threshold of 10-20\% leading to a 5 mm larger radius (i.e. one voxel) than that of the kidney volume, \( V_{K,\text{total}} \), estimated using the CT.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Measurement times (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>1.1 22 44 70 166</td>
</tr>
<tr>
<td>P2</td>
<td>1.3 18 66 163</td>
</tr>
<tr>
<td>P3</td>
<td>0.5 18 46 68 165</td>
</tr>
<tr>
<td>P4</td>
<td>2.2 19 47 67 164</td>
</tr>
<tr>
<td>P5</td>
<td>0.3 23</td>
</tr>
<tr>
<td>P6</td>
<td>0.3 21</td>
</tr>
<tr>
<td>P7</td>
<td>2.1 25</td>
</tr>
<tr>
<td>P8</td>
<td>0.4 22</td>
</tr>
<tr>
<td>P9</td>
<td>0.6 20</td>
</tr>
<tr>
<td>P10</td>
<td>0.2 20</td>
</tr>
<tr>
<td>P11</td>
<td>0.3 18</td>
</tr>
<tr>
<td>P12</td>
<td>0.3 21</td>
</tr>
<tr>
<td>P13</td>
<td>0.2 17</td>
</tr>
</tbody>
</table>

TABLE B.1. Patients measurement time post injection
C. Results

FIGURE 1. Example of typical fit (P1): PET (A) and therapy (B)
FIGURE 2. Fits of P5 (lowest $R^2$): PET (A) and therapy (B)
TABLE 1. Averaged estimated pharmacokinetic parameters of leave-one-out jackknife populations (PSA positive patients)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Organ</th>
<th>Parameter</th>
<th>Unit</th>
<th>Mean</th>
<th>SD</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMA receptor density</td>
<td>Kidneys</td>
<td>$[R_{K,0}]$</td>
<td>nmol·l⁻¹</td>
<td>16</td>
<td>4.3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Tumor lesion</td>
<td>$[R_{TU,0}]$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor REST</td>
<td>$[R_{TU,Rest,0}] = ([R_{TU,1,0}] + [R_{TU,2,0}])/2$</td>
<td></td>
<td>45</td>
<td>28</td>
<td>16-160⁺</td>
</tr>
<tr>
<td>Release rate</td>
<td>Kidneys</td>
<td>$\lambda_{K,release}$</td>
<td>min⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>$\lambda_{TU,release}$</td>
<td>min⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum flow density</td>
<td>$f_{TU,0}$</td>
<td>ml·min⁻¹·g⁻¹</td>
<td>0.14</td>
<td>0.12</td>
<td>0.1†</td>
</tr>
<tr>
<td></td>
<td>Tumor REST</td>
<td>$f_{TU,Rest}$</td>
<td>ml·min⁻¹·g⁻¹</td>
<td>0.06</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidneys</td>
<td>$f_{K} = f_{k,c} - 0.026 \cdot \text{Age}$</td>
<td>ml·min⁻¹·g⁻¹</td>
<td>4.0</td>
<td>0.39</td>
<td>4.3§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$f_{k,c}$</td>
<td>ml·min⁻¹·g⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each patient file was fitted separately using an iterative fitting. After each iteration, the mean and standard deviation were obtained and used as Bayesian information in the next step, until convergence. The pharmacokinetic information of the remaining tumor is contained in the total body scan and the PET measurement.

*Assuming densities of $10^8$- $10^9$ cells/ml [1] and 100,000 copies/cell [2]

† Derived using a PBPK for a sst2 specific $^{111}$In labeled ligand [3]

‡ Normally tumor blood flow ranges between 0.01-1.0 ml·min⁻¹·g⁻¹. 0.1 ml·min⁻¹·g⁻¹ is often used as typical e.g. for simulations studies [4]

§ [5]
**TABLE 2.** Coefficients of determination $R^2$ of the fits of total body, tumor lesion 1, tumor lesion 2 and the kidneys of all patients (without P7).

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Total body</th>
<th>Tumor lesion 1</th>
<th>Tumor lesion 2</th>
<th>Kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.98</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>P2</td>
<td>0.89</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>P3</td>
<td>0.73</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>P4</td>
<td>0.80</td>
<td>0.99</td>
<td>0.98</td>
<td>1.00</td>
</tr>
<tr>
<td>P5</td>
<td>0.91</td>
<td>0.77</td>
<td>0.40</td>
<td>0.94</td>
</tr>
<tr>
<td>P6</td>
<td>0.99</td>
<td>0.89</td>
<td>0.99</td>
<td>0.88</td>
</tr>
<tr>
<td>P8</td>
<td>0.96</td>
<td>0.94</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>P9</td>
<td>1.00</td>
<td>0.92</td>
<td>0.81</td>
<td>0.98</td>
</tr>
<tr>
<td>P10</td>
<td>0.99</td>
<td>0.87</td>
<td>0.97</td>
<td>1.00</td>
</tr>
<tr>
<td>P11</td>
<td>0.94</td>
<td>0.84</td>
<td>0.91</td>
<td>1.00</td>
</tr>
<tr>
<td>P12</td>
<td>0.94</td>
<td>0.95</td>
<td>0.86</td>
<td>0.92</td>
</tr>
<tr>
<td>P13</td>
<td>0.98</td>
<td>0.86</td>
<td>0.95</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**REFERENCES**

Modeling and predicting tumor response in radioligand therapy

Peter Kletting, Anne Thieme, Nina Eberhardt, Andreas Rinscheid, Calogero D’Alessandria, Jakob Allmann, Hans-Jürgen Wester, Robert Tauber, Ambros J Beer, Gerhard Glatting and Matthias Eiber

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