

**PhD Thesis Title:** “Investigation of PET-Based Treatment Planning in Peptide-Receptor Radionuclide Therapy (PRRT) Using a Physiologically Based Pharmacokinetic (PBPK) Model”

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## ABSTRACT:

Peptide-receptor radionuclide therapy (PRRT) for neuroendocrine tumors has shown to be an effective therapeutic option in addition to chemotherapy or external beam therapy. PRRT uses radiolabeled somatostatin analogues to target the somatostatin receptors (most commonly subtype 2 (sst<sub>2</sub>)) on neuroendocrine tumor cell surfaces. Several centers perform PRRT with standard doses. By this, the potential individual differences in biodistribution and resulting toxicities are neglected. Individualized treatment protocols could have the potential to further enhance the effect of targeted internal molecular radiotherapy. The advantage of patient-based compared to cohort-based treatment is difficult to assess in clinical trials, because especially the patient-based treatment planning is time consuming. Furthermore, the implementation of positron emission tomography (PET) measurements may help to increase the accuracy and efficiency of patient-based treatment planning in PRRT. Therefore, the importance of patient-based treatment planning and also the implementation of PET measurements in PRRT were investigated in this study.

In the first part of this simulation study, a recently developed physiologically based pharmacokinetic (PBPK) model was used to investigate the effect of different degrees of individualization for the prediction of the therapeutic time-integrated activity coefficients (TIACs), which determine the absorbed doses to the organs during molecular radiotherapy. The parameters of the PBPK model were fitted to the biokinetic data of 15 patients with metastasized neuroendocrine tumors after the injection of <sup>111</sup>In-DTPAOC to derive the assumed true model parameters. The mathematical phantoms of the patients were defined with increasing individualization levels to see at which level the prediction of the TIACs is accurate enough for therapy. As results, it can be concluded that:

1. Individualized treatment planning is needed, as the relative deviation (RD) of the TIACs between the true biokinetics and the biokinetics of the mean patient were extremely high, i.e., mean patient  $RD_{\text{tumor}}=(625\pm 1266)\%$  and  $RD_{\text{kidneys}}=(11\pm 38)\%$ .
2. The inclusion of patient specific data, e.g. height, weight, body mass index, tumor volume and glomerular filtration rate, do not suffice even when using a PBPK model, i.e., mean patient plus additional individual data  $RD_{\text{tumor}}=(-2\pm 27)\%$  and  $RD_{\text{kidneys}}=(16\pm 43)\%$ .
3. Integrating all available *a priori* information in the PBPK model and using additionally noiseless PET data measured at one time point for all organs could possibly be sufficient to perform an individualized treatment planning, i.e., mean patient plus additional data and one noiseless PET measurement  $RD_{\text{tumor}}=(-2\pm 22)\%$  and  $RD_{\text{kidneys}}=(-0.1\pm 0.5)\%$ .

In the second part of this study, simulated PET measurements for different protocols and noise were collected. The aim was to investigate the optimal protocol and noise level of PET measurements to allow accurate prediction of therapeutic TIACs. As result, two time-point measurements at 1 and 4 h p.i. can be used to predict the therapeutic biodistribution with an acceptable accuracy (variability of the TIAC  $\leq 10\%$ ) in our patient group. Accurate dosimetry can be performed for the kidneys with a noise level up to a fractional standard deviation of 1% in the PET measurements. Nevertheless, the sampling schedule and the effect of different degrees of noise in a real PET measurement data, with respect to the prediction accuracy, must be further investigated for a larger patient population.

Thus, using a PBPK model and mathematical patient phantoms, it could be demonstrated that a simple and, nevertheless, individual dosimetry may be possible based on individually acquired

PET data. Therefore, further measurements and developments in this direction are recommended to fully use the potential of PBPK modelling in molecular radiotherapy.

**References to author publications that relate specifically to the dissertation:**

1. **D. Hardiansyah**, C. Maass, A.A. Attarwala, B. Muller, P. Kletting, F.M. Mottaghy, and G. Glatting, "The role of patient-based treatment planning in peptide receptor radionuclide therapy," *European Journal Nuclear Medicine and Molecular Imaging* **43(5)**, 871-880 (2016).
2. **D. Hardiansyah**, W. Guo, P. Kletting, F.M. Mottaghy, and G. Glatting, "Time-integrated activity coefficients estimation for radionuclide therapy using PET and a pharmacokinetic model: A simulation study on the effect of sampling schedule and noise," *Med Phys* 43(9), accepted for the September 2016 issue.
3. **D. Hardiansyah**, N.J. Begum, P. Kletting, F.M. Mottaghy, and G. Glatting, "Sensitivity Analysis of a Physiologically Based Pharmacokinetic Model Used for Treatment Planning in Peptide Receptor Radionuclide Therapy," *Cancer Biotherapy and Radiopharmaceuticals* **31(6)**, 217-224 (2016).