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Investigation of PET-Based Treatment Planning in Peptide-Receptor Radionuclide Therapy (PRRT) Using a Physiologically Based Pharmacokinetic (PBPK) Model

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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_2)) 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 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 work, a recently developed 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 ^{111}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, e.g. mean patient RD_{tumor}=(625±1266)% and $RD_{kidneys}$=(11±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, e.g. mean patient plus additional individual data RD_{tumor}=(-2±27)% and $RD_{kidneys}$=(16±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, e.g mean patient plus additional data and one noiseless PET measurement RD_{tumor}=(-2±22)% and $RD_{kidneys}$=(-0.1±0.5)%.

In the second part of this work, simulated PET measurements for different protocols and noise were collected. The aim of this work was to investigate the optimal protocol and noise level of PET measurements to allow accurate prediction of therapeutic TIACs. As result, two time-point measurement at 1 and 4 h p.i. can be used to predict the therapeutic biodistribution with an acceptable accuracy (variability of the TIAC ≤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 in this work 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.