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Original paper

Prediction of time-integrated activity coefficients in PRRT using simulated dynamic PET and a pharmacokinetic model

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ABSTRACT

Purpose: To investigate the accuracy of predicted time-integrated activity coefficients (TIACs) in peptide-receptor radionuclide therapy (PRRT) using simulated dynamic PET data and a physiologically based pharmacokinetic (PBPK) model.

Methods: PBPK parameters were estimated using biokinetic data of 15 patients after injection of (152 ± 15) MBq of ^{111}In-DTPAOC (total peptide amount (5.78 ± 0.25) nmol). True mathematical phantoms of patients (MPPs) were the PBPK model with the estimated parameters. Dynamic PET measurements were simulated as being done after bolus injection of 150 MBq ^{68}Ga-DOTATATE using the true MPPs. Dynamic PET scans around 35 min p.i. (P_1), 4 h p.i. (P_2) and the combination of P_1 and P_2 (P_3) were simulated. Each measurement was simulated with four frames of 5 min each and 2 bed positions. PBPK parameters were fitted to the PET data to derive the PET-predicted MPPs. Therapy was simulated assuming an infusion of 5.1 GBq of ^{90}Y-DOTATATE over 30 min in both true and PET-predicted MPPs. TIACs of simulated therapy were calculated, true MPPs (true TIACs) and predicted MPPs (predicted TIACs) followed by the calculation of variabilities v.

Results: For P_1 and P_2 the population variabilities of kidneys, liver and spleen were acceptable ($v < 10\%$). For the tumours and the remainders, the values were large (up to 25%). For P_3, population variabilities for all organs including the remainder further improved, except that of the tumour ($v > 10\%$).

Conclusion: Treatment planning of PRRT based on dynamic PET data seems possible for the kidneys, liver and spleen using a PBPK model and patient specific information.

1. Introduction

Peptide-receptor radionuclide therapy (PRRT) is a frequently used method for the treatment of neuroendocrine tumours (NETs) [1,2]. The accuracy of activity quantification plays an important role in the PRRT treatment planning [3,4]. This quantification is based on measured individual biokinetics using planar scintigraphy data [1] or SPECT/CT [5]. It has been shown that positron emission tomography (PET) is more accurate for activity quantification as compared to planar scintigraphy [6] or SPECT, due to higher sensitivity and better spatial resolution [7]. For example, PET with ^{68}Ga-labelled somatostatin analogues has a high diagnostic accuracy and correlates with radionuclide uptake in PRRT [8–10]. However, up to now pre-therapeutic PET data were not used to predict the therapeutic time-integrated activity coefficients (TIACs) due to different affinities, amounts and short physical half-life of the used radiopharmaceuticals.

Previously we have shown in a simulation study that a *static* PET measurement with two time points at 1 and 4 h p.i. can possibly be used to predict the therapeutic biodistribution in the organ at risk, e.g. kidneys and liver with an acceptable accuracy [11]. Furthermore, it was demonstrated based on a simulation study that accurate dosimetry for the kidneys could possibly be performed for all relevant levels of noise [12]. However, treatment planning using *static* PET measurements at different time points is time consuming for both, patient and staff. Implementation of one *dynamic* PET measurement resolves this limitation as dynamic PET provides

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both spatial and temporal information on biokinetics of the measurement interval [13].

Therefore, the aim of this *in silico* study was to investigate the accuracy of predicted TIACs using simulated *dynamic* PET measurements and a published PBPK model with a certain population and individual parameters [14] for treatment planning of PRRT.

2. Material and methods

2.1. Patient data

Fifteen metastasized neuroendocrine tumour (NET) patients planned for four cycles of therapy with ^{90}Y-DOTATOC were included (Fig. 1 A). The same physiological and biokinetics patient data as in our previous study were used [15], which are described elsewhere [15].

2.2. PBPK model

A previously published PBPK model describing the biodistribution of sst2 specific peptides [14] was used to simulate and analyse the pre-therapeutic and therapeutic biodistribution of the radiolabelled species, i.e., ^{68}Ga-DOTATATE and ^{90}Y-DOTATATE respectively. The model includes detailed modelling of the organs: tumour, kidneys, spleen, liver and remainder. It includes labelled and unlabelled peptide systems with corresponding competition of binding to sst2. The internalization rate λ_{int}, dissociation rate k_{off}, dissociation constant K_D and the physical decay λ_{phys} were taken from the literature as shown in Table 1 [16–18].

Quality control of fits was checked by visual inspection of the graphs, observing the adjusted R^2 (near to 1) and the coefficient of variation of fitted parameters CV (CV < 25% corresponds to "precise", 25% < CV < 50% to "acceptable") [19].

2.3. Derivation of the true and PET-predicted MPPs

Fig. 1 shows the general workflow of the study. The PBPK model was implemented using simulation analysis and modelling software SAAMII v. 2.2 (The Epsilon Group, USA) [20]. Two types of mathematical patient phantoms (MPPs) were built for the analysis, i.e. true MPPs and PET-predicted MPPs.

True MPPs consisted of the PBPK model and a set of assumed true parameters. In brief, the following parameters were individually estimated from the patient data (Section 2.1): the fraction of filtered peptide f_{ex}, degradation rate of the peptide in each organ λ_{deg}, tumour perfusion f_{TU}, total number of receptor in each organ R_{organ}, glomerular filtration rate *GFR* and tumour volume V_{TU} (Fig. 1 C and F).

PopKinetic software (PopKinetic v. 2.2, The Epsilon Group, USA) [20] with the standard-two-stage (STS) method was implemented to derive the Bayesian parameters from the population (Fig. 1 D), by calculating the mean and standard deviation of the parameters

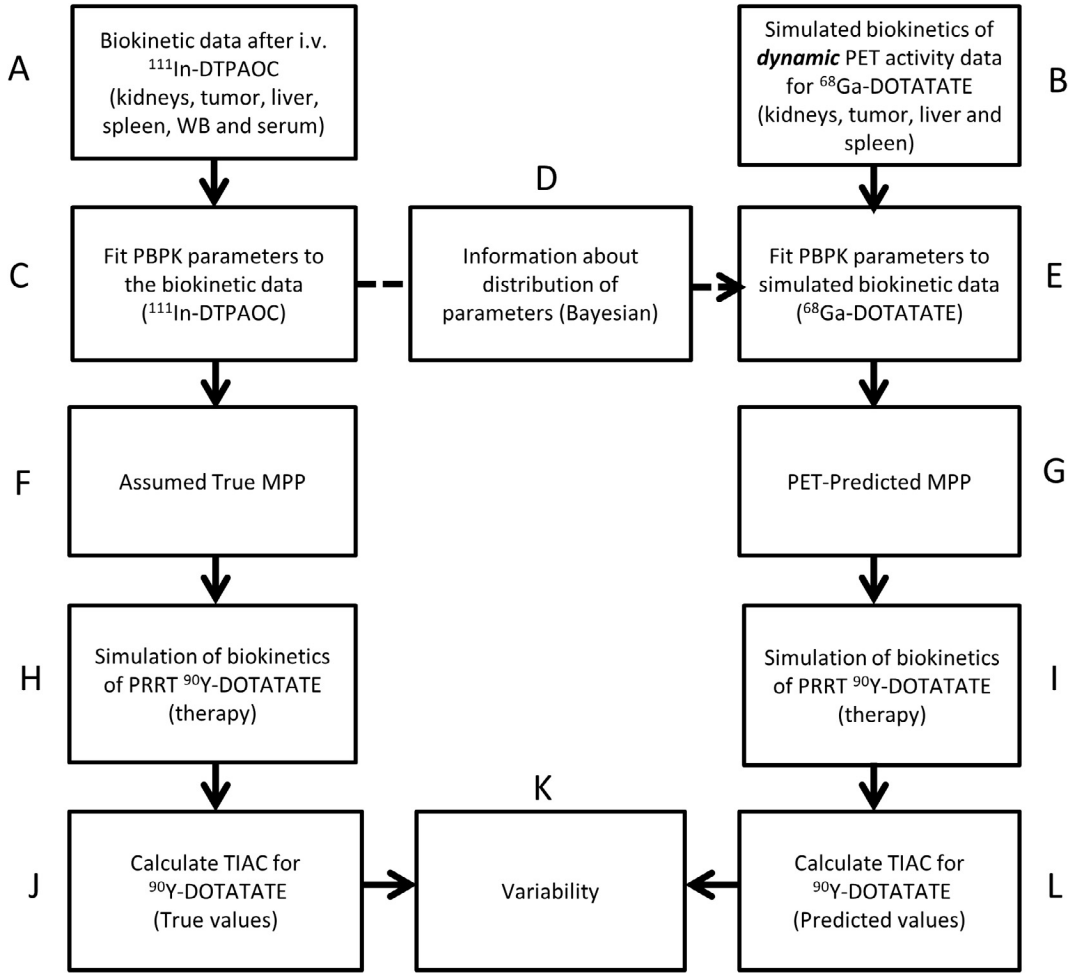

Fig. 1. Workflow of the performed fittings and simulations (Sections 2.3 and 2.4). PRRT: peptide-receptor radionuclide therapy; TIACs: time-integrated activity coefficients; PBPK: physiologically-based pharmacokinetic (model).

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