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SHORT COMMUNICATION

The cycle effect quantified: reduced tumour uptake in subsequent cycles of [^{177}Lu]Lu-HA-DOTATATE during peptide receptor radionuclide therapy

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Abstract

Background Clear evidence regarding the effect of reduced tumour accumulation in later peptide receptor radionuclide therapy (PRRT) cycles is lacking. Therefore, we aimed to quantify potential cycle effects for patients treated with [^{177}Lu]Lu-HA-DOTATATE using a population pharmacokinetic (PK) modelling approach.

Methods A population PK model was developed using imaging data from 48 patients who received multiple cycles of [^{177}Lu]Lu-HA-DOTATATE. The five-compartment model included a central, kidney, spleen, tumour and lumped rest compartment. Tumour volume and continued use of long-acting somatostatin analogues (SSAs) were tested as covariates in the model. In addition, the presence of a cycle effect was evaluated by relating the uptake rate in a specific cycle as a fraction of the (tumour or organ) uptake rate in the first cycle.

Results The final PK model adequately captured observed radioactivity accumulation in kidney, spleen and tumour. A higher tumour volume was identified to increase the tumour uptake rate, where a twofold increase in tumour volume resulted in a 2.3-fold higher uptake rate. Also, continued use of long-acting SSAs significantly reduced the spleen uptake rate (68.4% uptake compared to SSA withdrawal (10.5% RSE)). Lastly, a cycle effect was significantly identified, where tumour uptake rate decreased to 86.9% (5.3% RSE) in the second cycle and even further to 79.7% (5.6% RSE) and 77.6% (6.2% RSE) in the third and fourth cycle, respectively, compared to cycle one.

Conclusions Using a population PK modelling approach, the cycle effect of reduced tumour uptake in subsequent PRRT cycles was quantified. Our findings implied that downregulation of target receptors is probably not the major cause of the cycle effect, due to a plateau in the decrease of tumour uptake in the fourth cycle.

Keywords ^{177}Lu-HA-DOTATATE · Population pharmacokinetic model · PRRT · NONMEM · Cycle effect · Neuroendocrine tumours

Introduction

Peptide receptor radionuclide therapy (PRRT) has proven to be an effective and well-tolerated treatment for patients with advanced-stage neuroendocrine tumours (NETs) [1–3]. Disease control rates for this therapy with Lutetium-177 labelled to somatostatin analogues such as DOTATATE ([^{177}Lu]Lu-DOTATATE) or high affinity DOTATATE ([^{177}Lu]Lu-HA-DOTATATE) are around 80% [4, 5] and many attempts have already been made to improve this treatment, for example by dosimetry-guided treatment individualization [6–8]. These approaches currently focus on not exceeding absorbed radiation dose limits to critical organs (i.e. prevent toxicity) rather than achieving high tumour accumulation for optimal treatment efficacy.

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Ideally, refining PRRT should focus on achieving optimal efficacy accompanied with acceptable toxicity while taking changes in absorbed doses over cycles into account. To accomplish such an approach, first, detailed knowledge on the differences in tumour and organ accumulation over cycles is required.

Currently, a standard dosing schedule for [^{177}Lu]Lu-(HA-)DOTATATE consists of four cycles of ~7.4 GBq with an interval of 8–12 weeks. Radiobiological effects of the treatment are already expected after the first cycle, since emission of beta radiation will result in DNA damage and thus immediate damage to cells [9]. Regarding the effects on tumours, it is emphasized that absorbed doses in tumours might be reduced in subsequent cycles due to these therapeutic effects (further referred to as the 'cycle effect'). This hypothesis is based on an initial study by Garkavij et al., where tumour absorbed doses decreased over cycles in 21 patients that received [^{177}Lu]Lu-DOTATATE whereas kidney accumulation remained largely unchanged [10]. Additional evidence for this phenomenon was recently provided in two retrospective trials [11, 12], though exact decreases in uptake between all different cycles was not yet quantified. By using a population pharmacokinetic (PK) modelling approach, quantification of the cycle effect on tumour uptake can be based on population data (with simultaneous modelling of all individual data and also including patients that did not receive all cycles). Other advantages of using this approach is that whole-body accumulation is considered while estimating the cycle effect and variability between individuals will be taken into account as well. Lastly, this methodology enables distinction between unexplained inter-cycle variability (i.e. parameters change randomly over cycles) and a structural cycle effect (i.e. a consistent parameter reduction). To provide additional (quantitative) knowledge regarding the cycle effect, the effect of reducing tumour uptake over cycles for patients treated with [^{177}Lu]Lu-HA-DOTATATE (which is used in routine clinical care in our hospital) was quantified using a population PK modelling approach.

Methods

Population pharmacokinetic model

Retrospective data of 48 patients receiving [^{177}Lu]Lu-HA-DOTATATE in our hospital were used to develop an empirical population PK model. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute in Amsterdam, the Netherlands (IRBd21-187). All patients received ~7.4 GBq [^{177}Lu]Lu-HA-DOTATATE followed by post-treatment imaging, where the majority of patients received one SPECT/CT at 24 h post injection and nine patients also received four planar scintigraphy scans at 0.5, 4, 24, and 72 h post injection. Patient selection, data acquisition and data analysis were described previously [13, 14]. Patient characteristics are shown in Table 1.

A five-compartment model was developed, where a similar approach as our previously developed model for [^{177}Lu]Lu-PSMA-617 was used [15]. Model compartments one to five represented a central compartment, kidneys, spleen, tumour and a rest tissue compartment, respectively. Organ volumes were derived from the ICRP Publication 89 adult human model [16]. The tumour compartment (and the according tumour volume) represented all segmented target tumours, which included a maximum of five segmented lesions with a diameter >2 cm (max. two per organ system) per patient. Tumour volumes were assessed with a 45% SUL_{max} threshold method on diagnostic [^{68}Ga]Ga-HA-DOTATATE PET/CT using IntelliSpace Portal (Philips Healthcare, The Netherlands).

The model accounted for inter-individual variability (IIV) on PK parameters and a residual unexplained variability (RUV), as was described before [15]. The renal excretion rate (k_{10}) and volume of the central compartment (V1) were fixed to 0.306 h^{-1} and 7.63 L, respectively, since no blood samples were available to estimate these parameters [17]. Inter-cycle (or 'cycle-to-cycle') variability was tested on uptake rate parameters, to assess whether a general variability on accumulation in organ and tumour compartments between cycles exists. Allometric scaling was added to all PK parameters [18]. Tumour volume was assessed as a covariate to impact the uptake rate in tumours (k_{14}) (similarly as described for [^{177}Lu]Lu-PSMA-617 [15]) and kidney (k_{12}). In addition, the effect of continued use of long-acting

Table 1 Patient characteristics

Characteristic	Median (range) or number (%)
Included patients (n)	48
Males (n)	22 (45.8%)
Age (years)	68 (44 – 85)
Weight (kg)	74 (46 – 108)
Primary tumour location (n)	
Small intestine	24 (50.0%)
Pancreas	9 (18.8%)
Digestive tract other than small intestine	8 (16.7%)
Lung	2 (4.2%)
Medullar thyroid carcinoma	1 (2.1%)
Unknown	4 (8.3%)
Tumour volume of segmented tumours (mL)	82.5 (7.81 – 393)
Injected radioactivity (MBq)	7424 (3950 – 7746)
Cycles with continued SSAs (n)	77 (44.5%)

somatostatin analogues (SSAs) during PRRT (administration <6 weeks prior to PRRT) on organ (k_{12} and k_{13}) and tumour (k_{14}) accumulation was evaluated [14]. To provide definite evidence regarding the existence of the cycle effect (i.e. reduced accumulation in subsequent cycles), all cycles were tested as dichotomous covariates on uptake in kidney (k_{12}), spleen (k_{13}), and tumours (k_{14}) by means of relating the uptake rate in a cycle as a fraction of the uptake rate in the first cycle, according to Eq. 1.

$$P_{cov} = P_{pop} * {\theta_{cov1}}^{cycle2} * {\theta_{cov2}}^{cycle3} * {\theta_{cov3}}^{cycle4} \quad (1)$$

where P_{cov} is the estimated individual uptake parameter value, P_{pop} is the estimated population uptake parameter value, and θ_{cov} values represent the estimated parameter value for that cycle as a fraction of P_{pop} (i.e. a fraction of the uptake rate in the first cycle).

Selection of the final model was guided the change in objective function value (−2 times the log likelihood, dOFV), parameter precision and by evaluation of goodness-of-fit plots and visual predictive checks [19]. In case of hierarchical nested models, a p-value <0.01 was considered a significant improvement of the model fit (corresponding to a decrease in OFV of ≥6.63 points following a Chi-square distribution with 1 degree of freedom).

Software

The modelling was performed using NONMEM (version 7.5; ICON development Solutions, Ellicott City, MD) using the first-order conditional estimation method with interaction (FOCE-I) and ADVAN13. R (version 4.2.1) was used for visualization of predictions of the final PK model.

Results

An overview of the model structure is provided in Fig. 1. The final first-order population PK model adequately described uptake in kidney, spleen, and tumours (see Fig. 2). All final PK parameter estimates are provided in Table 2. Tumour volume was added as a covariate to the tumour uptake rate (k_{14}) (using a power function with an estimated value of 1.13), where a twofold increase in tumour volume resulted in a 2.3-fold higher tumour uptake rate. Tumour volume had no impact on the kidney uptake rate (k_{12}). In addition, the continued use of long-acting SSAs significantly impacted the uptake rate for spleen (k_{13}), where it decreased to 68.4% in case of continued use of SSAs compared to spleen uptake rates in patients with SSA withdrawal. No effect of continued use of long-acting SSAs was identified on kidney and tumour uptake rates. Lastly, the cycle effect was significantly identified during PRRT with [^{177}Lu]Lu-HA-DOTATATE.

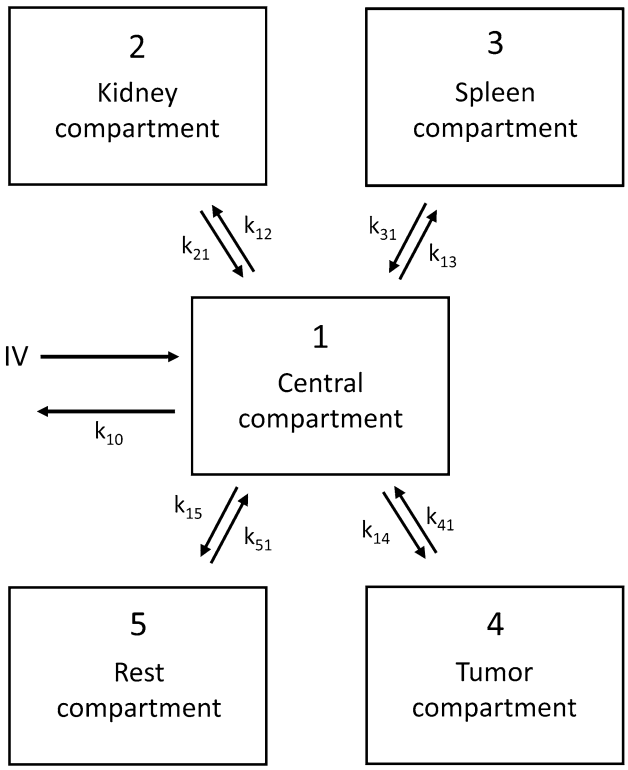


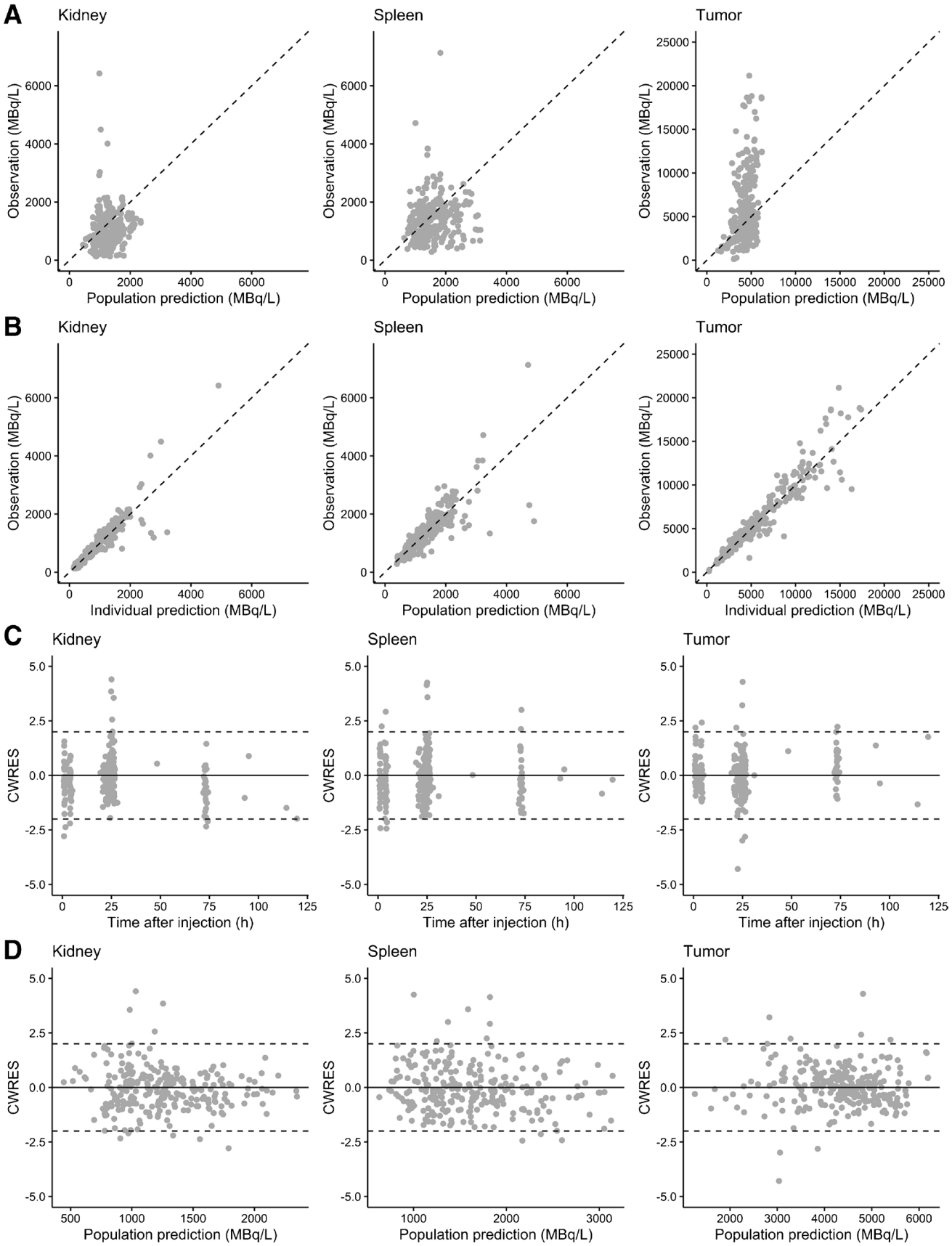
Fig. 1 Overview of the five-compartment population PK model for [^{177}Lu]Lu-HA-DOTATATE

The tumour uptake rate decreased to 86.9% in the second cycle and even further to 79.7% and 77.6% in the third and fourth cycle, respectively, compared to cycle one. Additionally, IIV was included on the cycle effect and was estimated rather small (38.6% CV). A graphical representation of all identified effects on [^{177}Lu]Lu-HA-DOTATATE accumulation is presented in Fig. 3.

Discussion

A population PK model was developed for [^{177}Lu]Lu-HA-DOTATATE based on data from 48 patients. Our covariate analysis identified a higher tumour uptake rate for patients with larger tumours, a decreased spleen uptake rate in case of continued use of SSAs and a cycle effect for tumours, where the uptake rate in tumours reduced over subsequent cycles.

The cycle effect was estimated as a fraction of the uptake in the first treatment cycle, thus absolute differences in reductions over cycles between patients with different tumour volumes are taken into account (see Fig. 3). Although the cycle effect was quantified, exact (radiobiological) mechanisms that cause this effect are not yet completely understood. A likely and previously hypothesized cause of reduced tumour accumulation over cycles could


A
Kidney
Spleen
Tumor
Observation (MBq/L)
Population prediction (MBq/L)
B
Kidney
Spleen
Tumor
Observation (MBq/L)
Individual prediction (MBq/L)
Population prediction (MBq/L)
C
Kidney
Spleen
Tumor
CWRES
Time after injection (h)
D
Kidney
Spleen
Tumor
CWRES
Population prediction (MBq/L)

◂**Fig. 2** Goodness-of-fit plots based on the final population PK model for [^{177}Lu]Lu-HA-DOTATATE, representing including population predictions (PRED) versus observations (**A**), individual predictions (IPRED) versus observations (**B**), conditional weighted residuals (CWRES) versus time after injection (**C**), and CWRES versus PRED (**D**), for the kidney, spleen, and tumour compartments separately

be decreased receptor expression in later cycles [10]. This assumption states that therapeutic radiation effects could damage the target receptors, even though the receptor and radiopharmaceutical dissociate intracellularly after internalization [20]. However, a recently performed study by Schiavo Lena et al. showed that the expression of somatostatin receptor 2A after PRRT in patients with pNETs remained very high, which does not support this hypothesis [21]. In addition, our plateau in tumour uptake rates in the third and fourth cycle also questions this hypothesis, since a further decrease in accumulation would be expected in every additional cycle due to the continued radiation exposure decreasing the target receptors every time [^{177}Lu]Lu-HA-DOTATATE is administered. Other plausible explanations for the reduced tumour accumulation over cycles are the direct effects of radiation on the tumour cells (e.g. cell necrosis, fibrosis, altered vascularization or a reduction of the tumour volume) [11, 12, 21, 22]. A cycle effect was not identified for spleen, whereas for kidney a slight increase in kidney uptake rates was estimated for the third and fourth cycle (both 16% increase) compared to cycle one. This might be due to a reduced tumour accumulation in those cycles and contributes to a smaller therapeutic window in later PRRT cycles.

This study has some limitations. First, partial volume effect (PVE) corrections were not performed on SPECT data and thus the PVE could potentially impact our estimations, especially due to small lesions (<37 mm diameter [23]). To reduce the influence of PVE on tumour uptake, while still including clinically relevant tumours, lesions <20 mm diameter were not included as input for the tumour compartment. Secondly, it was not investigated how the cycle effect might be affected by individual factors, such as gender, tumour type, tumour grade, or previous treatment. By including more patient data in future research, we hope to distinguish between different groups and potentially identify differences in the quantified cycle effect. However, IIV on this cycle effect was rather small, indicating that clinically relevant different cycle effects among patients are not expected. Gained knowledge regarding the cycle effect is crucial in case one would individualize PRRT based on post-administration imaging. Apparently, absorbed tumour doses decrease over cycles and dosimetry-based treatment individualization based on the first cycle is not representative for tumour accumulation in later cycles. In addition, the therapeutic window of PRRT becomes smaller in later cycles, which should be considered in case of optimizing treatment protocols. Therefore, to achieve optimal treatment response, the best approach might be to increase the injected radioactivity in the initial cycles to improve exposure in case of optimal tumour uptake. Another, less favorable, approach could be to increase the administered activity in later cycles (to achieve similar tumour exposure compared to cycle one). However, particularly considering the smaller therapeutic window, accumulation in critical organs should be assessed to prevent exceeding absorbed dose limits and causing unwanted toxicity. Furthermore, our findings implied that the downregulation of target receptors is probably not the major cause of reduced tumour absorbed doses in later cycles. This is an important aspect for potential re-treatment with PRRT in patients with progressive disease, since remaining tumour

Table 2 Parameter estimates based on the final population PK model for [^{177}Lu]Lu-HA-DOTATATE in patients with NETs, with five compartments representing a central compartment, kidney, spleen, tumour, and a rest tissue compartment, respectively

Pharmacokinetic parameters	Estimate (RSE%)	95% CI
Structural parameters		
k_{10} (h^{-1})	0.306[a]	
k_{12} (h^{-1})	2.38 (14.1%)	1.81 – 3.16
k_{21} (h^{-1})	0.813 (7.4%)	0.704 – 0.931
k_{13} (h^{-1})	1.47 (12.9%)	1.16 – 1.91
Continued long-acting SSAs on k_{13}[b]	0.684 (10.5%)	0.559 – 0.843
k_{31} (h^{-1})	0.732 (7.5%)	0.636 – 0.847
k_{14} (h^{-1})	1.87 (15.8%)	1.37 – 2.50
Tumour volume on k_{14}[c]	1.18 (9.6%)	0.950 – 1.40
Cycle 2 on k_{14}[b]	0.869 (5.3%)	0.775 – 0.954
Cycle 3 on k_{14}[b]	0.797 (5.6%)	0.707 – 0.881
Cycle 4 on k_{14}[b]	0.776 (6.2%)	0.680 – 0.877
k_{41} (h^{-1})	0.512 (8.1%)	0.439 – 0.605
k_{15} (h^{-1})	23.1 (8.4%)	19.7 – 27.3
k_{51} (h^{-1})	0.506 (4.0%)	0.468 – 0.549
V1 (L)	7.63[a]	
V2 (male / female) (L)	0.310 / 0.275[a]	
V3 (male / female) (L)	0.150 / 0.130 [a]	
Inter-individual variability		
k_{12} (CV%)	66.4 (19.6%)	56.2 – 80.8
k_{13} (CV%)	61.6 (20.0%)	52.6 – 75.6
k_{14} (CV%)	74.6 (22.5%)	61.6 – 93.1
Cycle effect (CV%)	38.6 (30.5%)	28.1 – 50.3
Residual unexplained variability		
Proportional error (CV%)	21.4% (6.3%)	20.2 – 22.8

[a]Fixed parameter

[b]Added as fractional change

[c]Added using a power covariate function

95% CI and RSE values were obtained from the SIR. *CI* confidence interval, *CV%* coefficient of variation, *RSE* relative standard error, *SIR* sampling importance resampling, *V1* central volume of distribution, *V2* kidney volume, *V3* spleen volume

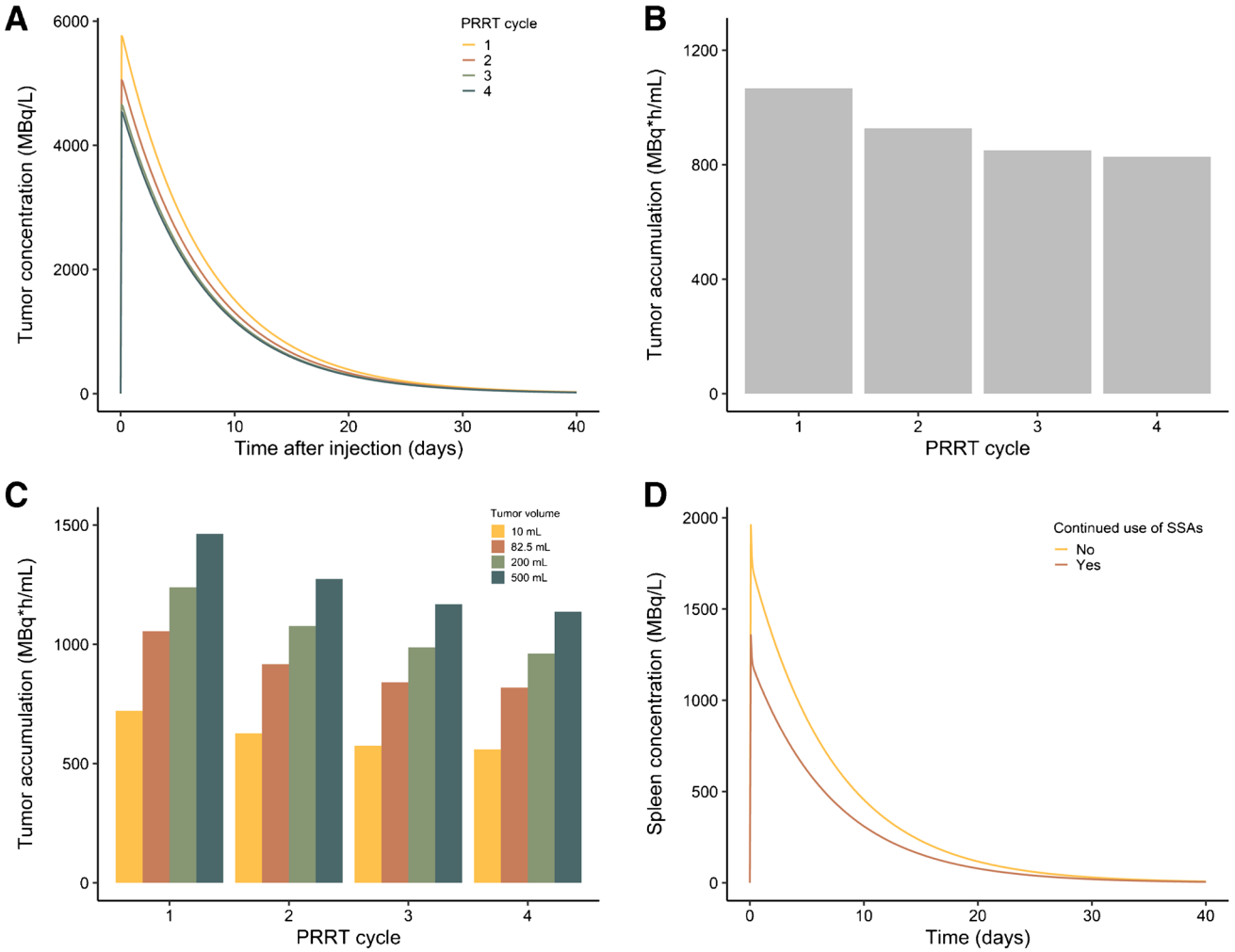


Fig. 3 Graphical representation of identified effects that impact [^{177}Lu]Lu-HA-DOTATATE uptake in spleen and tumour (based on simulations of one typical patient with median patient characteristics), where the cycle effect on tumour concentrations and accumulation during peptide receptor radionuclide therapy (PRRT) (**A**, **B**), the effect of individual tumour volume on tumour accumulation per PRRT cycle (**C**), and the effect of continued use of somatostatin analogues (SSAs) on spleen uptake (**D**) are shown

receptor expression is required for [^{177}Lu]Lu-DOTATATE tumour accumulation and thus treatment efficacy.

Conclusions

The developed population pharmacokinetic model adequately captured observed accumulation in kidney, spleen, and tumour lesions for patients with NETs receiving [^{177}Lu]Lu-HA-DOTATATE. Spleen uptake rate decreased to 68.4% for patients with continued use of long-acting somatostatin analogues during PRRT cycles (whereas kidney and tumour uptake rates were not affected). The effect of reduced tumour uptake over cycles was identified and was estimated to decrease to 86.9% in the second cycle and even further to 79.7% and 77.6% in the third and fourth cycle, respectively, compared to the first cycle. The observed plateau in decrease of tumour uptake in the fourth cycle implied that downregulation of target receptors is probably not the major case of the cycle effect.

Author contributions HS, JJMAH, and BJdW contributed to the study conception and design. HS developed the model and HS, JJMAH, and ADRH discussed the modelling methodology. HS, JJMAH, BJdW, ADRH, and DMVH contributed to the interpretation of the results. The first draft of the manuscript was written by HS. All authors provided critical review on previous versions of the manuscript and approved the final manuscript.

Data availability The datasets used for the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval 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. Informed consent was obtained from all individual participants included in the study. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute in Amsterdam, the Netherlands (IRBd21-187).

Consent to participate Informed consent was obtained via institutional procedures from all individual participants included in the studies (of which data were used for model evaluation).

Consent to publish Not applicable.

Competing interests The authors declare no competing interests.

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