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Clinical Pharmacokinetics of Radiopharmaceuticals from SPECT/CT Image Acquisition by Contouring in Patients with Gastroenteropancreatic Neuroendocrine Tumors: Lu-177 DOTATATE (Lutathera®) Case

Anissa Barakat^{1,2,3} · Lore Santoro^{3,4} · Myrtille Vivien^{5,6} · Pierre-Olivier Kotzki^{3,4} · Emmanuel Deshayes^{3,4} · Sonia Khier^{1,2} 

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Abstract

Background and Objective Lu-177 DOTATATE (Lutathera®) is a radiolabeled analog of somatostatin administered intravenously in patients with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. Biodistribution of Lu-177 DOTATATE in tumor and healthy tissues can be monitored by serial post-injection scintigraphy imaging. Patient exposure to the drug is variable with the recommended fixed dosage, and hence there is a variable response to treatment. The aim of this work was to study the pharmacokinetics of Lu-177 DOTATATE by a population modeling approach, based on single-photon emission computed tomography (SPECT)/computed tomography (CT) images used as surrogate of plasma concentrations to study the interindividual variability and finally optimize an individual dosage.

Methods From a retrospective study, SPECT/CT images were acquired at 4 h, 24 h, 72 h, and 192 h postadministration. From these images, volumic activities were calculated in blood and bone marrow. An individual non-compartmental pharmacokinetic analysis was performed, and the mean pharmacokinetic parameters of each tissue were compared together and with reference data. Blood volumic activities were then used to perform a population pharmacokinetic analysis (NONMEM).

Results The pharmacokinetic parameters (non-compartmental analysis) obtained from blood (clearance [CL] = 2.65 L/h, volume of distribution at steady state [V_{ss}] = 309 L, elimination half-life [t_{1/2}] = 86.3 h) and bone marrow (CL = 1.68 L/h, V_{ss} = 233 L, t_{1/2} = 98.8 h) were statistically different from each other and from reference values (CL = 4.50 L/h, V_{ss} = 460 L, t_{1/2} = 71.0 h) published in the literature. SPECT/CT blood images were used as a surrogate of plasma concentrations to develop a population pharmacokinetic model. Weight was identified as covariate on volume of the central compartment, reducing the interindividual variability of all population pharmacokinetic parameters.

Conclusion This study is a proof of concept that obtaining pharmacokinetic parameters with image-based blood concentration is possible. Obtaining observed concentrations from SPECT/CT images, without the need for blood sampling, is a real advantage for the patient and the drug monitoring. Pharmacokinetic modeling could be combined with a deep learning model for automatic contouring and allow precise patient-specific dose adjustment in a non-invasive manner.

✉ Sonia Khier
sonia.khier@umontpellier.fr

¹ Pharmacokinetics and Pharmacometrics Department, School of Pharmacy, UFR Pharmacie, Montpellier University, 15 Avenue Charles Flahault, 34000 Montpellier, France

² Probabilities and Statistics Department, Institut Montpelliérain Alexander Grothendieck (IMAG), CNRS, UMR 5149, Inria, Montpellier University, Montpellier, France

³ Nuclear Medicine Department, Montpellier Cancer Institute, Montpellier University, Montpellier, France

⁴ Institut de Recherche en Cancérologie de Montpellier (IRCM), INSERM U1194, Montpellier University, Montpellier, France

⁵ Biostatistics, Informatics and pharmaceutical physic Laboratory, School of Pharmacy, UFR Pharmacie, Montpellier University, 15 Av. Ch. Flahault, 34000 Montpellier, France

⁶ Institute of Functional Genomic (IGF)- UMR 5203, INSERM U1191, Montpellier, France

Key Points

Pharmacokinetic parameters (non-compartmental analysis) evaluated from images of the blood and the bone marrow are statistically different from each other and from the reference values (Phase III NETTER-1).

However, from a clinical point of view, the average pharmacokinetic parameters calculated from the concentrations of the aorta images were consistent with the reference values.

The population pharmacokinetic model explained part of interindividual pharmacokinetic variability by a relationship between volume of distribution and weight.

The sources of interindividual variability need to be explored more specifically aiming for a better precision dosing.

1 Introduction

Lu-177 DOTATATE (Lutathera®) is a radiolabeled peptide used in targeted radionuclide therapy. Lu-177 DOTATATE is composed of a somatostatin analog coupled to a radionuclide (Lutetium-177). The structure is presented by Hennrich and Kopka [1]. Lutetium-177 is an artificial radionuclide with a physical half-life of 6.647 days. Lutetium is the last member of the lanthanide family. Its +3 oxidation state leads to specific chemical properties with the ability to be taken by chelates in a very stable way (here 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid: DOTA). It decays with co-emission of both beta-minus particles responsible for radiobiological effects after interaction with water or cell compounds ($E_{\max} = 497$ keV [abundance 78.6%], 384 keV [9.1%], 176 keV [12.2%] and gamma photons, 208 keV [11.1%], 113 keV [6.6%]). The latter may be detected by gamma-cameras performing planar (2D) or SPECT (3D) scintigraphy. Lu-177 DOTATATE has been approved by the European Medicine Agency in 2017 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET) in adults. The recommended dosage for Lu-177 DOTATATE (i.e., quantity of activity injected) is a fixed prescription of 7.4 GBq every 8 weeks (Q8W) administered as an intravenous (IV) injection, for a total of 4 injections. In case of strong adverse reactions, the prescribed activity is resumed to 3.7 GBq for

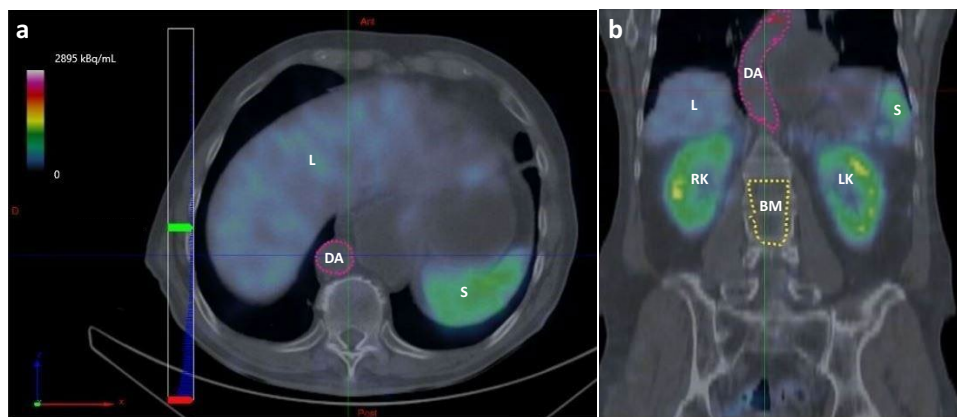
the next cycle after full recovery; otherwise the treatment is stopped.

Effects (efficacy or toxicity) of targeted radionuclide therapies like Lu-177 DOTATATE are linked to DNA damage caused (directly or indirectly) by ionizing radiation leading to cell deaths [2]. These effects are related to a physical parameter: the absorbed dose in tissues, expressed in Gy, which is a quantity of energy (J) released in a specific mass (kg). Calculating the absorbed dose in targeted radionuclide therapy is challenging. Indeed, one has to take into consideration physical parameters (i.e., physical half-life, emitted particles, energy of disintegration, etc.) but also individual biological parameters including patient-specific radioactivity accumulations in the organs or tumors of interest and their masses. Due to the emission of gamma particles during the disintegration process, the spatial and temporal distribution of Lutetium-177 may be approached by performing for each patient multiple noninvasive postinjection imaging to finally calculate the absorbed dose.

A large interindividual variability (IIV) in terms of bio-distribution is described by time–activity curve shape in the healthy tissues and tumor uptake [3] for Lu-177 DOTATATE. This suggests a potential pharmacokinetic IIV of Lu-177 DOTATATE and, consequently, the possibility of therapeutic ineffectiveness or side effects such as nephrotoxicity [4] and hematotoxicity [5] due to a nonoptimal dosage. Optimizing dosage requirements is an important challenge. Even if it is not the standard schema of treatment, various studies have proposed dosimetry-based methods individually adjust the quantity of Lu-177 DOTATATE to be administered [6, 7]. Pharmacokinetic modeling, especially the population pharmacokinetic (PopPK) approach, is an indispensable tool used in drug development to explore the potential sources of pharmacokinetic and pharmacodynamic IIV and to help in making decisions at critical stages, for example, optimizing dosage requirements, and recently, a review has shown the great potential of the pharmacokinetic modeling of the radiopharmaceuticals [8]. Usually, the PopPK models are based on observed concentration values obtained from blood samples. Blood tests are not part of the clinical routine for the patient treated with Lu-177 DOTATATE, but after injection of Lu-177 DOTATATE, body imaging may be performed with single-photon emission computed tomography (SPECT) and computed tomography (CT). These images are noninvasive observations used for dosimetry assessment to evaluate the absorbed dose to organs-at-risk and tumors. Therefore, we used these SPECT/CT routine images processed with a specific calibration, as surrogate of plasma concentrations of Lu-177 DOTATATE to elaborate a PopPK model.

Another objective of this work was to compare two methods of drug quantification and drug monitoring: drug concentrations obtained from biological samples (blood

Fig. 1 Contouring of the descending aorta (DA) and bone marrow (BM) for quantification. Performed on the PLANET Dose software. a: axial plane and b: coronal plane of a hybrid SPECT/CT imaging. Anatomical information is given by computed tomography (CT) and functional information by nuclear medicine scintigraphy. *L* liver, *RK* right kidney, *LK* left kidney, and *S* spleen



sampling) *versus* drug concentrations obtained by imaging (contouring), comparing pharmacokinetic parameters.

2 Methods

2.1 Patients

Patients with GEP-NET treated with Lu-177 DOTATATE at the nuclear medicine department of the Regional Cancer Institute of Montpellier (ICM, France) and who performed postinjection multiple SPECT/CT images for dosimetric calculations between May 2016 and January 2020 could be included in this retrospective study. Patients with poor quality of SPECT/CT images (unreadable, reconstruction failure, important background noise) were excluded from the study. The study protocol (LUTAPOP) was approved by the local Ethics Committee Review Board of the Regional Cancer Institute of Montpellier (ICM-ART 2023/01). The study was carried out in accordance with the principles of the Declaration of Helsinki for medical research on human subjects.

2.2 Demographic and Clinical Data

From the medical records, we selected and collected clinical and biological data that we considered as potential covariates explaining pharmacokinetic variability to be integrated in the PopPK analysis.

2.3 Drug Administration

The prescribed dosage of ¹⁷⁷Lu-DOTA-TATE (Lutathera, Advanced Accelerator Applications, a Novartis company) was 7.4 GBq via intravenous infusion over 40 min Q8W for a total of up to 4 injections. The Lu-177 DOTATATE physical decay and the residual activity remaining in the

vial have been considered to quantify the exact activity administered to each patient.

2.4 Data Acquisition

As literature does not mention any validated protocol for calculating blood concentration from imaging, we proposed to use the Lu-177 DOTATATE concentration obtained from SPECT/CT of the descending aorta (DA) and the bone marrow (BM) to compare our results with those obtained by Forrer et al. [9].

All imaging acquisitions were performed using the SPECT/CT Discovery NM/CT 670 system (General Electric [GE] Healthcare) including a Bright Speed 16 CT scanner and 3/8-in NaI(Tl) crystal thickness, according to the acquisition protocol described by Santoro et al. [10]. SPECT/CT fields of view, from the top of the liver to the sacrum, were acquired at 4 h, 24 h, 72 h, and 192 h after the first and second injection. For injections 3 and 4, a single SPECT/CT acquisition could be performed 24 h after injection based on medical considerations.

After the last SPECT/CT image acquisition at 192 h, all SPECT/CT data were reconstructed using the “Volumetrix MI Evolution for oncology”, an application from Xeleris Software (General Electric [GE] Healthcare) and exported to the treatment planning system PLANET Dose (DOSIsoft SA, Cachan, France).

BM contouring consisted in delineating the trabecular section on the L2–L4 lumbar vertebrae, considering that this section represents 6.7% of the total BM [11]. The DA was delineated from the aortic arch to the iliac bifurcation (Fig. 1). At each time point, the volumic activity inside the BM and the DA was quantified. For this purpose, the number of counts given by SPECT/CT images were converted into activity using the calibration factor previously obtained [10]. The volumes of both segmented organs (DA and BM) were collected from the software. To correct the partial volume effect, inducing an underestimation of quantification in small volume (< 46 cc), a previously determined recovery

coefficient [10] was applied to the activity encountered in this segmented volume.

The volumic activities (Bq/cc) of Lu-177 DOTATATE in the DA and BM extracted from the SPECT/CT have been used as tissue concentrations to calculate the pharmacokinetic parameters of Lu-177 DOTATATE. The latter parameters have been compared together and to the parameters of reference by statistical analysis. After evaluation of the accuracy of using DA volumic activities to estimate the blood concentrations, this data has been used to build the PopPK model.

2.5 Pharmacokinetic Analysis

2.5.1 Individual Pharmacokinetic Analyses

Individual pharmacokinetic explorations were carried out by non-compartmental analysis (NCA) using PKanalix (version 2019 R1) [12]. Lu-177 DOTATATE mean observed pharmacokinetic parameters—elimination half-life ($t_{1/2}$), volume of distribution at steady state (V_{ss}), and clearance (CL)—have been obtained for both the BM and the DA. Elimination half-life is the time required to divide the plasma concentration by two after reaching pseudo-equilibrium (steady state), calculated on the terminal part of the concentration time curve.

2.5.2 Statistical Analysis of the Individual Pharmacokinetic Data

Statistical analyses of the pharmacokinetic parameters obtained from the NCA have been conducted with R (version 3.5.0) and R studio software (version 1.3.1093). Before t -test, an ANOVA test was applied to ensure that there were no effects that would confound the results.

Explored factors were injection number (first versus second), nature of the studied tissues (BM versus DA), and patient. Patients with one or more missing pharmacokinetic parameters have been excluded from the ANOVA. Then, to evaluate whether the pharmacokinetic parameters of Lu-177 DOTATATE obtained from SPECT/CT were representative of those obtained from blood samples, we performed a bilateral univariate t -test. The analysis has been conducted on the pharmacokinetic parameters (CL, V_{ss} , $t_{1/2}$) for DA and BM obtained by NCA and were compared with the reference data published by the Food and Drug Administration (FDA) in the highlights of prescribing information document [13]. The patients included in the t -test had to be independent; therefore, the averaged parameters over different treatments have been used when a patient had received more than once the treatment.

2.5.3 Population Pharmacokinetic Modeling

PopPK analysis was conducted using the nonlinear mixed-effects model running on NONMEM (version 7.4.1), with Perl-speaks-NONMEM (PsN) toolkit (version 4.7.0) and its first-order conditional estimation method with interaction (FOCE-I). An R package (PopkinR) [14] was used as NONMEM interface. The DA volumetric activities evaluated in the previous step have been used as observed concentrations (dependent values). The potential covariates obtained as possibly involved in the IIV from clinical and demographic data are presented and listed in Table 1. The PopPK model building was based on a three-stage method: first, we determined the structural and errors models, then we screened and selected covariates, and finally, we performed a bootstrap and a visual predictive check (VPC) to evaluate the model performance and stability and to qualify the PopPK model. Different structural models have been explored (one-, two-, and three-compartment(s) models with first-order elimination from the central compartment). The random IIV of pharmacokinetic parameters was estimated using an exponential-error model, as shown in Eq. 1:

$$P_{ij} = \theta_p \times e^{\eta_i} \quad (1)$$

P_{ij} is the parameter value for the i th individual on the j th occasion, θ_p is the typical value for the pharmacokinetic parameter in the study population, η_i is the random IIV, and κ_j the random interoccasion variability. Residual variability was evaluated according to an additive and/or proportional error model. The choice of the structural model selected was made by a comparison of the objective function value (OFV) with $OFV = -2 \times \log(\text{likelihood})$ and the Akaike information criterion (AIC) with $AIC = OFV + 2 \times N_p$ (N_p = number of parameters). For both, the lower value has been retained. Evaluation criteria were also the successes of minimization, the confidence intervals (CI) of the estimated parameters (alpha risk = 5%), and the adequacy of goodness-of-fit plots. The success rate reflected also the stability of the model. All pathological and physiological conditions potentially involved in the IIV have been explored as the covariates and listed in Table 1. The relationship between these conditions and the structural model parameters was tested with several mathematical relationships using the “stepwise covariate modeling” building tool of PsN [15] with the parallel states option. In the forward stepwise, any covariate that reduced the OFV to 6.64 at least ($p < 0.01$, chi-squared test with one degree of freedom) was considered significantly correlated to a pharmacokinetic parameter and added to the model. If more than one covariate was significant, the covariate retained was the one resulting in the greatest decrease of the OFV. The remaining covariates were tested again in subsequent forward steps until no

Table 1 Demographics, biological characteristics, and pathological conditions of patients included in the study

Variable	Number (%)	Median [min–max]	Mean (\pm SD)
Age (years)		66 [41–82]	66 (\pm 10)
Weight (kg)		72 [38–163]	75 (\pm 24)
Sex			
Female	12 (41)		
Male	17 (59)		
Size (cm)		172 [156–195]	174 (\pm 9)
Body mass index (kg/m ²)		23 [15–48]	24 (\pm 6)
Creatinine clearance <i>CKD-EPI</i> (mL/min/1.73 m ²)		70 [46–105]	71 (\pm 14)
Co-treatment with somatostatin analog	22 (76)		
Primary tumor location			
<i>Ileum</i>	21 (73)		
<i>Pancreas</i>	5 (17)		
<i>Unknown</i>	3 (10)		
Metastasis	26 (90)		
Bone metastasis	10 (38)		
Antigen KI-67 (%)		5.5 [1–30]	7.4 (\pm 6.3)
Blood chromogranin A concentration (ng/mL)		211 [33–43 000]	2300 (\pm 8500)
Tumor grade			
<i>1</i>	7 (24)		
<i>2</i>	20 (69)		
<i>3</i>	1 (3)		
<i>Unknown</i>	1 (3)		
External radiotherapy	3 (10)		
Tumor surgery	18 (62)		
Radioembolization	11 (38)		
Krenning score			
<i>3</i>	10 (34)		
<i>4</i>	19 (66)		

SD standard deviation

additional covariate significantly improved the model. In the backward-elimination process, if the deletion of a covariate increased the OFV to 10.8 or less ($p < 0.001$, chi-squared test with one degree of freedom), the covariate was removed from the model. Several criteria of the final model predictive performance have been evaluated. The mean prediction error (MPE) was an indicator of bias (Eq. 2), and the root mean square error (RMSE) was a measure of the precision (Eq. 3):

$$MPE = \frac{1}{N} \sum_{t=1}^N (C_{pred} - C_{obs}) \quad (2)$$

$$RMSE = \sqrt{\frac{\sum_{i=1}^N (C_{pred} - C_{obs})^2}{N}} \quad (3)$$

C_{pred} is the predicted concentration, C_{obs} is the observed concentration, and N is the number of observations. An internal evaluation of the final model was carried out with

a VPC based on 1000 simulations. The 5th, 50th, and 95th percentiles of C_{obs} and C_{pred} from the model were compared. The observed data percentiles had to be included in the CI (95%) of the simulated data percentiles. Median values and the corresponding 95% CI of the parameter estimates were computed from the analysis of 1000 bootstrap datasets, generated by random sampling with replacement from the original dataset using PsN toolkit [16].

3 Results

3.1 Patients

Of the 33 eligible patients, 5 were excluded, and 28 were included in the study. Of the patients, 27 had received one treatment (maximum of 4 injections), and 1 patient had received the treatment twice (8 injections) in total (Fig. 2). From the clinical and demographic data, we retained 18

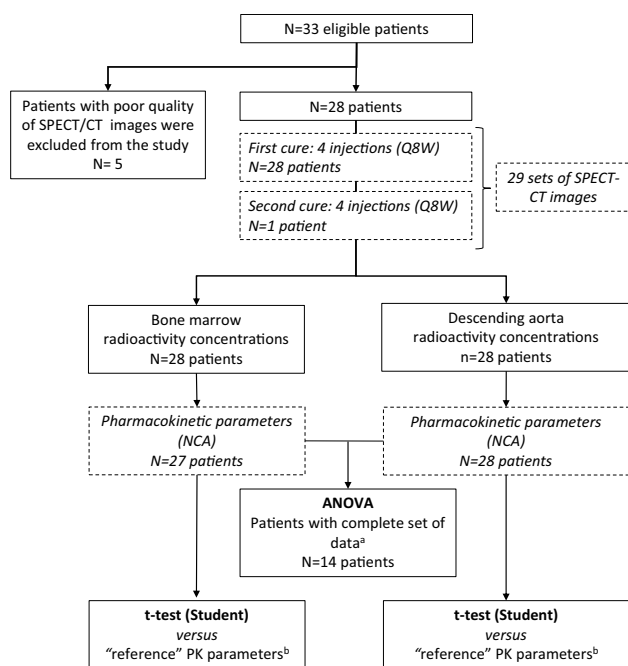


Fig 2 Flowchart of patients' inclusion in the statistical and pharmacokinetic analyses. a: patients with one missing pharmacokinetic (PK) parameter (from bone marrow or descending aorta) were excluded of the ANOVA; b: published in the European public assessment reports [13]. NCA non-compartmental analysis

Table 2 Interaction of the factors (patient, tissue type, and injection number) on the pharmacokinetic parameters

Factor	CL	V _{ss}	$t_{1/2}$
Injection number	0.587	0.062	0.455
Patient	0.031	$3.54 \cdot 10^{-3}$	0.074
Tissue	$7.22 \cdot 10^{-6}$	$2.12 \cdot 10^{-4}$	$8.41 \cdot 10^{-3}$
Injection number:patient	0.633	0.227	0.405
Injection number:tissue	0.469	0.595	0.579
Patient:tissue	0.131	$5.96 \cdot 10^{-3}$	0.066

Results are the p -values of ANOVA

CL clearance, V_{ss} total volume of distribution at steady state, $t_{1/2}$ elimination half-life

potential covariates as possibly involved in the IIV, 17 of these covariates are presented in the Table 1, and the other covariate tested was the number of the injection (first versus second).

3.2 Statistical Analysis of the Individual Pharmacokinetic Parameters

ANOVA test has been conducted on 14 patients. From these results (Table 2), we concluded that the only significant interaction is the "patient:tissue" interaction on V parameter

($p < 0.05$). Volume of distribution is significantly different according to the patient and the tissue. Moreover, these results also reveal no statistically significant effect from injection number (first versus second) on pharmacokinetic parameters (CL, V, and $t_{1/2}$). However, a significant effect of the nature of the tissue (BM versus DA) on pharmacokinetic parameters was demonstrated ($p < 0.05$; Table 2), suggesting that BM cannot be used as a surrogate of plasma concentrations. A significant effect on patient ($p < 0.05$) for CL and V_{ss} parameters appeared, too.

The t -test has been conducted on 28 patients; for patients who have received the treatment twice, the mean parameters of both treatments have been used. The pharmacokinetic parameters were averaged over the first and the second injection, as we demonstrated that there is no impact of the injection number on their value. The mean pharmacokinetic parameters calculated of each tissue (BM or DA) were then compared with the reference parameters published by the FDA [13]. The univariate t -test revealed that the mean pharmacokinetic parameters obtained by NCA of the image-based DA concentrations were significantly different (alpha risk = 5%) from the reference pharmacokinetic parameters. We obtained the same results for the BM (Table 3).

3.3 Population Pharmacokinetic Model

A two-compartment model with first-order elimination was the most appropriate model to describe the observed data obtained by SPECT/CT of DA. The PopPK parameters were the clearance (CL), the intercompartmental clearance (Q), the volume of the central compartment (V₁), and the volume of the peripheral compartment (V₂). Residual error could be described by a proportional model (OFV = 941, AIC = 959) or a combined proportional and additive model (OFV = 941, AIC = 961). Therefore, the proportional model has been retained per parsimony principle. After both the forward and the backward stepwise, we observed that the weight (WT) was significantly correlated to the volume of the central compartment (V₁) following the mathematical relationship shown in Eq. 4:

$$V_1 = (1 + \theta_{V_1} \times (WT - WT_{median})) \quad (4)$$

A comparison between PopPK parameters of the structural model and the final model is presented in Table 4. The estimated pharmacokinetic parameters did not present any significant correlation (confidence interval 95%), and the minimization of the model was always successful. Final model parameters have been estimated with a satisfying precision (relative standard error [RSE] < 50%) except the IIV on Q (RSE of 51.35%). Adding the covariates to the model decreased the IIV of every pharmacokinetic parameter (Table 4).

Table 3 Comparison of the mean of the observed pharmacokinetic parameters with the reference pharmacokinetic parameters (*t*-test)

Tissue	Pharmacokinetic parameter	<i>N</i>	Mean [min–max]	Reference value ^a mean (CV)	<i>P</i> -value ^b
Bone marrow	CL (L/h)	26	1.68 [0.411–3.02]	4.50 (31%)	< 2.20.10 ⁻¹⁶
Bone marrow	V _{ss} (L)	26	233 [53.0–395]	460 (54%)	7.09.10 ⁻¹⁵
Bone marrow	<i>t</i> _{1/2} (h)	26	98.8 [68.1–155]	71.0 (40%)	3.96.10 ⁻⁹
Descending aorta	CL (L/h)	28	2.65 [1.09–5.86]	4.50 (31%)	1.24.10 ⁻¹⁰
Descending aorta	V _{ss} (L)	28	309 [118–576]	460 (54%)	6.34.10 ⁻⁸
Descending aorta	<i>t</i> _{1/2} (h)	28	86.3 [41.2–220]	71.0 (40%)	0.0310

^aData published in the European public assessment report (EPAR) of Lutathera[13]

^bAlpha risk = 5% and (*N* – 1) degrees of freedom

N Number of patients, *CV* coefficient of variation, *CL* clearance, *V*_{ss} total volume of distribution at steady state, *t*_{1/2} elimination half-life.

Table 4 Population parameters of the base and the final model

Population parameter	Structural model		Final model		
	Estimate value (CV, %)	% RSE	Estimate value (CV, %)	% RSE	Bootstrap Median [95% CI]
CL (L/h)	2.68	4.99	2.71	4.80	2.61 [2.28–2.96]
V1 (L)	77.9	8.18	77.2	7.67	75.2 [60.4–91.4]
Q (L/h)	6.78	9.84	6.59	9.70	6.80 [4.96–9.11]
V2 (L)	190	7.80	188	7.28	189 [157–226]
Effect of WT on V1	–	–	0.015	12.8	0.017 [0.006–0.02]
Interindividual variability					
ω ² CL	0.116 (35%)	21.6	0.109 (34%)	22.3	0.101 [0.0462–0.178]
ω ² V1	0.231 (51%)	28.9	0.103 (33%)	48.6	0.130 [1.032 × 10 ⁻⁵ –0.331]
ω ² Q	0.167 (43%)	38.1	0.122 (36%)	51.35	0.0657 [1.22 × 10 ⁻⁵ –0.231]
ω ² V2	0.249 (53%)	30.1	0.198 (47%)	34.2	0.146 [0.0488–0.293]
Residual variability					
ε ²	0.028 (17%)	27.0	0.039 (20%)	24.3	0.06 [0.045–0.072]

%RSE = (100×SE/Estimate). *RSE* relative standard error, *CV* coefficient of variation calculated considering log-normal variability for parameters using $CV(\%) = \sqrt{e^{\omega^2}} - 1 * 100$, *CI* confidence interval, *CL* clearance, *V1* volume of the central compartment, *Q* intercompartmental clearance, *V2* volume of the peripheral compartment

The bootstrap 95% CIs reflect the range of estimates from the final model; these ranges are relatively narrow except for V1 and Q. The goodness-of-fit plots (Fig. 3) showed that population (PRED) and individual (IPRED) predicted concentrations were in a good agreement with the observed concentrations. The conditional weighted residual versus time plot showed satisfying predictions over the time for the first and the second injections. The VPC plot showed that the different percentiles (5th, 50th, 95th) of the observed concentrations were close to the simulated data for the first and the second injections (Fig. 4). For 1000 bootstrap samples, the convergence rate was 83.3%, suggesting a good stability of the PopPK model. The final model's mean bias (MPE) and precision (RMSE) for IPRED were –4.28% and 22.7%, respectively, better than those computed for PRED, which were –6.86% and 49.6%, respectively.

4 Discussion

The purpose of this retrospective study was to explore pharmacokinetic IIV of the Lu-177 DOTATATE by population approach. To this purpose volumic activities obtained by SPECT/CT were used as a surrogate of plasma concentrations that were not available in clinical routine. The first challenge was to estimate the blood concentrations with image-based quantification of tissues. From a clinical perspective, the most relevant tissue to approximate blood concentration was the DA. Therefore, Lu-177 DOTATATE's DA concentrations were collected, but as no protocol was validated for this method, it was first necessary to evaluate the relevance of the data obtained from the images. To evaluate the similarity of pharmacokinetic profiles obtained by imaging with those obtained from

Fig 3 Goodness-of-fit plots of the final model. **a**: population predicted concentrations (PRED) versus observed concentrations (C_{obs}); **b**: individual predicted concentrations (IPRED) versus observed concentrations (C_{obs}), conditional weighted residual (CWRES) versus time; **c**: for the first injection; **d**: for the second injection

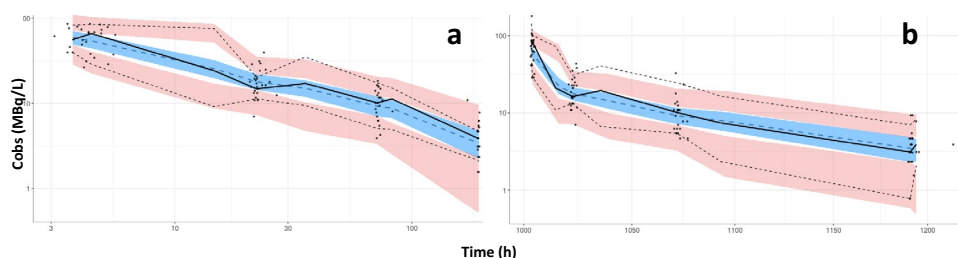
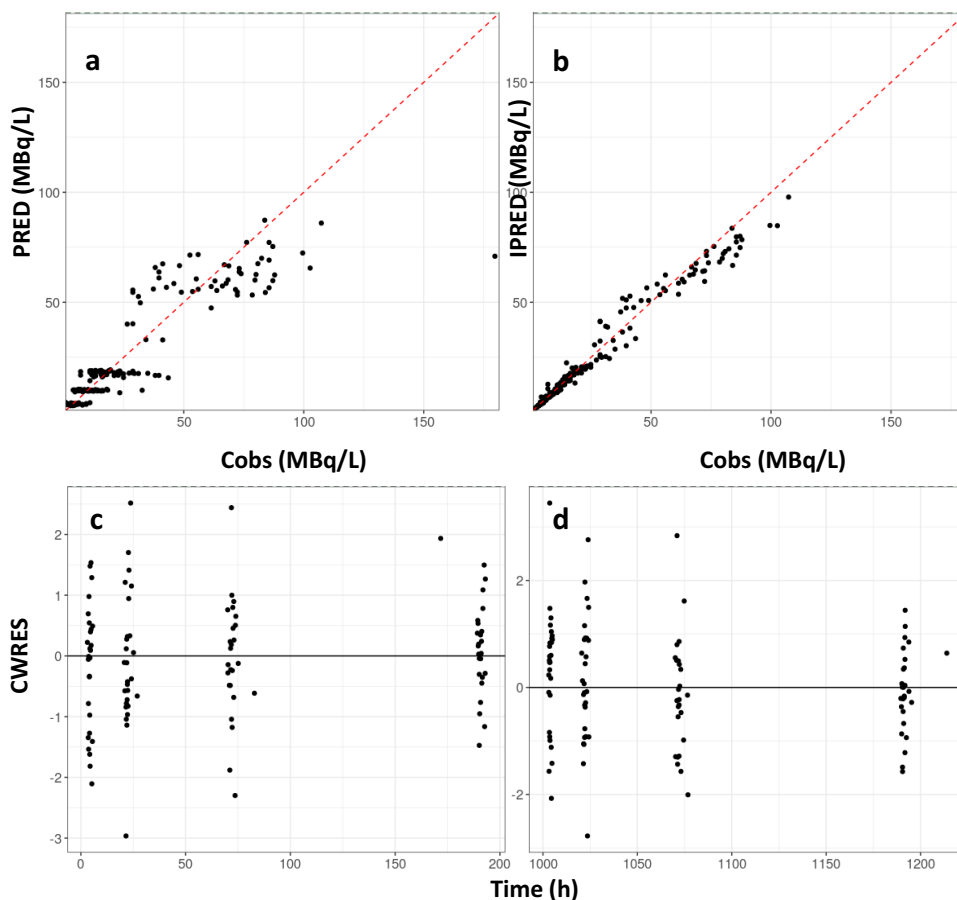


Fig 4 Visual Predictive Check (VPC) based on 1000 simulations for the first (**a**) and the second injection (**b**). Black dots represent observed concentrations on DA images (C_{obs}), and lines represent the 5th percentile (down, dotted), the 95th percentile (up, dotted), 50th percentile (middle, solid) of the observations and the 50th percentile

of the predictions (middle, dotted). Pink areas represent 95% confidence interval of the 5th percentile (down) and the 95th percentiles (up) of the predictions, and the blue area represents the 95% confidence interval of the 50th percentile of the predictions. **a**: first injection; **b**: for the second injection

biological samples, pharmacokinetic parameters obtained from DA images were compared with literature parameters (t -test). As a previous study conducted by Forrer et al. showed that the radioactivity concentration of Lu-177 DOTATATE in the BM was identical to that in the blood (based on biological samples) [9], we also collected the Lu-177 DOTATATE concentration from the BM images.

We found that the pharmacokinetic parameters evaluated from images of the DA and the BM were statistically

different from each other. In Forrer et al. [9], Lu-177 DOTATATE concentrations have been obtained from radioactivity measurements of BM aspirations and blood samples with none of patients having bone metastasis. In our study, we estimated the Lu-177 DOTATATE concentrations by analyzing SPECT/CT images: for BM the Lu-177 DOTATATE concentrations were collected from the lumbar spine (L2–L4) of patients with ($N = 4$) or without bone metastasis ($N = 6$), considering this section as representative of the

total bone marrow. However, for patients who had tumors in contact with L2–L4 vertebrae or L2–L4 vertebral metastases, Lu-177 DOTATATE concentrations from images focused on L2–L4 might be wrongly representative of those from the total BM. In addition, as shown by Linn Hagmarker et al. [17], the mere presence of bone metastasis, wherever they are, could influence the bone marrow concentrations and absorbed dose determined by image-based methods.

Thus, to evaluate if the pharmacokinetic parameters of Lu-177 DOTATATE in BM and DA obtained by analysis of SPECT/CT images are homogenous, it would be useful to repeat this study on patients without bone metastasis in the explored BM area to avoid a potential misestimating of concentrations. However patient recruitment may be difficult because Lu-177 DOTATATE is prescribed for advanced disease. Also, to perform the ANOVA, we needed for each patient the list of the observed pharmacokinetic parameters for both injections (first and second) and both tissues (DA and BM). At least one of the parameters was missing for 14 patients; therefore we conducted the ANOVA on 14 patients only. The test would be more relevant if we could have more included patients.

We also found that the pharmacokinetic parameters of DA and BM were statistically different from the reference values of the pharmacokinetic parameters indicated in the highlights of prescribing information published by the FDA [13]. These pharmacokinetic parameters have been obtained with a clinical study conducted on 20 patients enrolled in the Phase III NETTER-1. The statistical analysis (*t*-test) results showed that the pharmacokinetic parameters obtained from the DA images were significantly different from the pharmacokinetic parameters of reference [13]. The difference between the image-based parameters and the reference parameters could be due to a difference in methodology used for the calculation of the parameters (NCA, individual modeling, number of samples, etc.) and quantification method. Indeed, we did not find any information on the methodology used for the data collection, dosage, and the pharmacokinetic parameters estimation in NETTER-1. The difference could also be explained by a small number of patients enrolled in the studies— $N = 20$ in our study and $N = 28$ in NETTER-1—and the high IIV highlighted by PopPK results. For further studies, a validation of our methodology of blood quantification based on images of the DA would be necessary. Collecting both blood samples and SPECT/CT images of the DA at the same time on the same patients and comparing the concentrations of Lu-177 DOTATATE would be a solution to validate the method of quantification by imaging. Anyway, from a clinical point of view the mean pharmacokinetic parameters calculated with the concentrations from the DA images were in the same order of magnitude with reference values although the values are statistically different.

Therefore, we have used the volumic activity collected from the SPECT/CT images of the DA to develop a PopPK model. The aim of the PopPK model was to explain why Lu-177 DOTATATE exposure varies greatly among patients, in other words explaining a part of the IIV to individualize the Lu-177 DOTATATE treatment. The IIV on V1 decreased from 51% to 33% adding the relationship between V1 and weight in the model. A previous PopPK model developed with blood concentration of Lu-177 DOTATATE based on blood samples has also shown a correlation between the weight and V1 in the intermediate model but not in the final model [18]. Physiologically the relationship between the weight and V1 is relevant. In our study, the weight has been measured only during the initial visit, but this parameter can vary greatly over the time especially for patients with cancer; it may be necessary to weigh the patients before each treatment injection. Those results show that variability on distribution could be explored more precisely to optimize dosage.

As a part of the IIV remains unexplained, exploring other potential covariates such as the density of somatostatin receptors on tumor cells [19] seems to be necessary. In any case, it is essential to increase the number of patients included in the analysis to enable better quantification of the between subject variability and a better assessment of the parameters-covariates' relationships. As the pharmacokinetic results are rare, in the future this analysis could be used as a prior knowledge within a Bayesian framework [20, 21] to support the estimation of the pharmacokinetic parameters. This preliminary work has demonstrated the possibility to exploit imaging in PopPK modeling. It is important to point out that SPECT/CT images performed for the dosimetry evaluation after Lu-177 DOTATATE administration are planned in the framework care. And as it is a non-invasive method of quantification, it is an interesting alternative for the patient to avoid blood samples. The Lu-177 DOTATATE quantification based on SPECT/CT images is a rich source of information offering many possibilities. For example, imaging can provide activity concentrations in several tissues inaccessible for samples such as tumor (to assess pharmacodynamics) sites or healthy tissues (to assess toxicokinetics). The images could also allow the biodistribution to be followed in real time with dynamic images. But to use image-based quantification in modeling, two important limits need to be solved in the future. The first one is the fact that the SPECT/CT cannot determine which form of the compound is detected. In the European public assessment report published by the European Medicines Agency [22], it is mentioned that the Lu-177 DOTATATE is poorly metabolized and mainly excreted in the urine as an intact compound. Therefore, we have considered that the radioactivity detected by the SPECT/CT corresponded to the initial form of the Lu-177 DOTATATE. But a recent study has shown that 24 h after the administration the major

part of the radioactivity in the plasma was consisting of metabolites of the Lu-177 DOTATATE [23]. If this last information is confirmed, it will be important to identify the structure of the metabolites of Lu-177 DOTATE and also to distinguish the radioactivity emitted from Lu-177 DOTATATE or its metabolites. Indeed, the effect of this treatment is exclusively related to the radioactive part of the compound, but the efficacy/toxicity balance depends on the integrity of the vector binding to its target. If metabolites exist (i.e., modified or detached vectors from 177-Lu) and are significant, the radioactivity detected via SPECT/CT images cannot be directly correlated to efficacy. The second one concerns the method of quantification of Lu-177 DOTATATE with SPECT/CT. The delineation procedure or contouring is typically performed manually, which exposes a major issue: reproducibility. But it is important to define a standard for the manual procedure. If the method is reproducible, it would allow comparison of the results obtained by different sites, and it will eventually offer the possibility to pool the results. To this end, guidelines for the quantification of 177Lu with SPECT/CT published by Ljungberg et al. could be useful. In it, they describe the limiting factors and propose associated recommendations [24]. Deep learning models for automatic contouring of tissues on radiotherapy CT images could also be explored as a time-saving and accurate tool for contouring in clinic practice.

The PopPK modeling is a powerful tool that could be a milestone for the development of a personalized targeted radionuclide therapy. With a robust model, it would be possible, for example, to simulate the concentration in organs-at-risk and lesions at late time based on the early images. Thus, with the combination of a PopPK model and a dosimetric study, it would be possible to use the data from the first injection to estimate the absorbed dose after the 2nd, 3rd, and 4th injections, which could be a great improvement for patient safety. Also, with the possibility to predict the pharmacokinetic at late time (e.g., 192 h) with the early SPECT/CT images (e.g., 4 h, 24 h), it would be possible to avoid the late images and thus greatly facilitate the patient journey.

5 Conclusion

To our knowledge, this study is the first PopPK model based on body images used as a surrogate of blood concentrations. The Lu-177 DOTATATE pharmacokinetic parameters obtained were clinically coherent with the reference values, demonstrating that blood concentrations derived from SPECT/CT images are an interesting alternative to blood samples that must be further explored. Our PopPK model reveals that the volume of the central compartment is correlated to the body weight. This preliminary work confirms that it is imperative to enhance the personalized approach

with PopPK models. On the road to precision medicine, it is urgent to exploit the rich information from molecular imaging in pharmacokinetic analysis of radioactive and non-radioactive compounds.

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Declarations

Conflict of interest All the authors declare that they have no financial nor non-financial interests that are directly or indirectly related to the work submitted for publication.

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Author contributions AB extracted and collected the data, analyzed the data, analyzed literature, and wrote the initial draft of the manuscript. LS contributed to the literature search, data extraction, and writing of the manuscript. MV supervised the statistical analysis and reviewing the manuscript. POK contributed to reviewing the manuscript. ED contributed to data extraction, provided clinical input, and reviewed the manuscript. SK conceptualized the study, contributed to literature research, supervised the pharmacokinetic analysis, and wrote the manuscript.

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