

A Population Pharmacokinetic Model Using Imaging Data to Assess Variability in Pharmacokinetics of ¹⁷⁷Lu-PSMA-617 in Low Volume Metastatic Prostate Cancer Patients

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INTRODUCTION

- Lutetium-177 Prostate Specific Membrane Antigen (¹⁷⁷Lu-PSMA) has shown its therapeutic effect in metastatic prostate cancer (PCa)¹
- Studies regarding evaluating and optimizing treatment have focused on individual patient data
- Little research has been conducted into population trends of ¹⁷⁷Lu-PSMA uptake
- Population PK modeling might be a promising tool to enhance quantification of ¹⁷⁷Lu-PSMA uptake based on post-treatment scans

AIM

- To explore the potential of using ¹⁷⁷Lu-PSMA-617 uptake data derived from SPECT/CT scans as input for population PK models
- To develop a population PK model to assess variability in organ and tumor uptake of ¹⁷⁷Lu-PSMA-617 in patients with low volume metastatic PCa

METHODS

- N = 10
- Study patients included from Radboud hospital in Nijmegen (NCT03828838)²
- Two cycles of ¹⁷⁷Lu-PSMA-617 with 8 week interval
- Administered activity: ~3 GBq and ~6 GBq
- 9 blood samples and 5 SPECT/CT scans after each administration
- Radioactivity concentrations corrected for decay
- NONMEM version 7.4

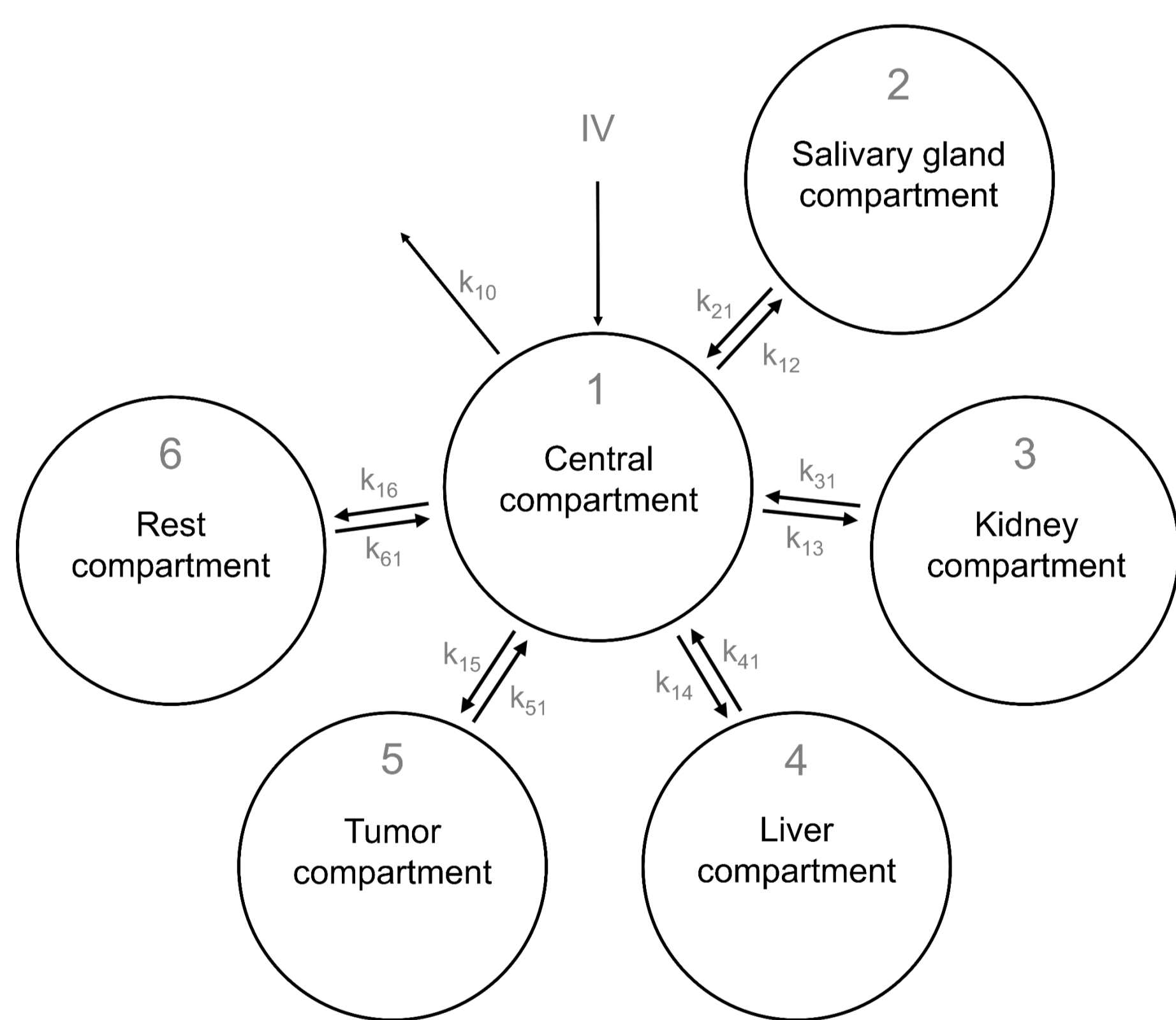


Fig 1. Overview of the six compartment model structure.

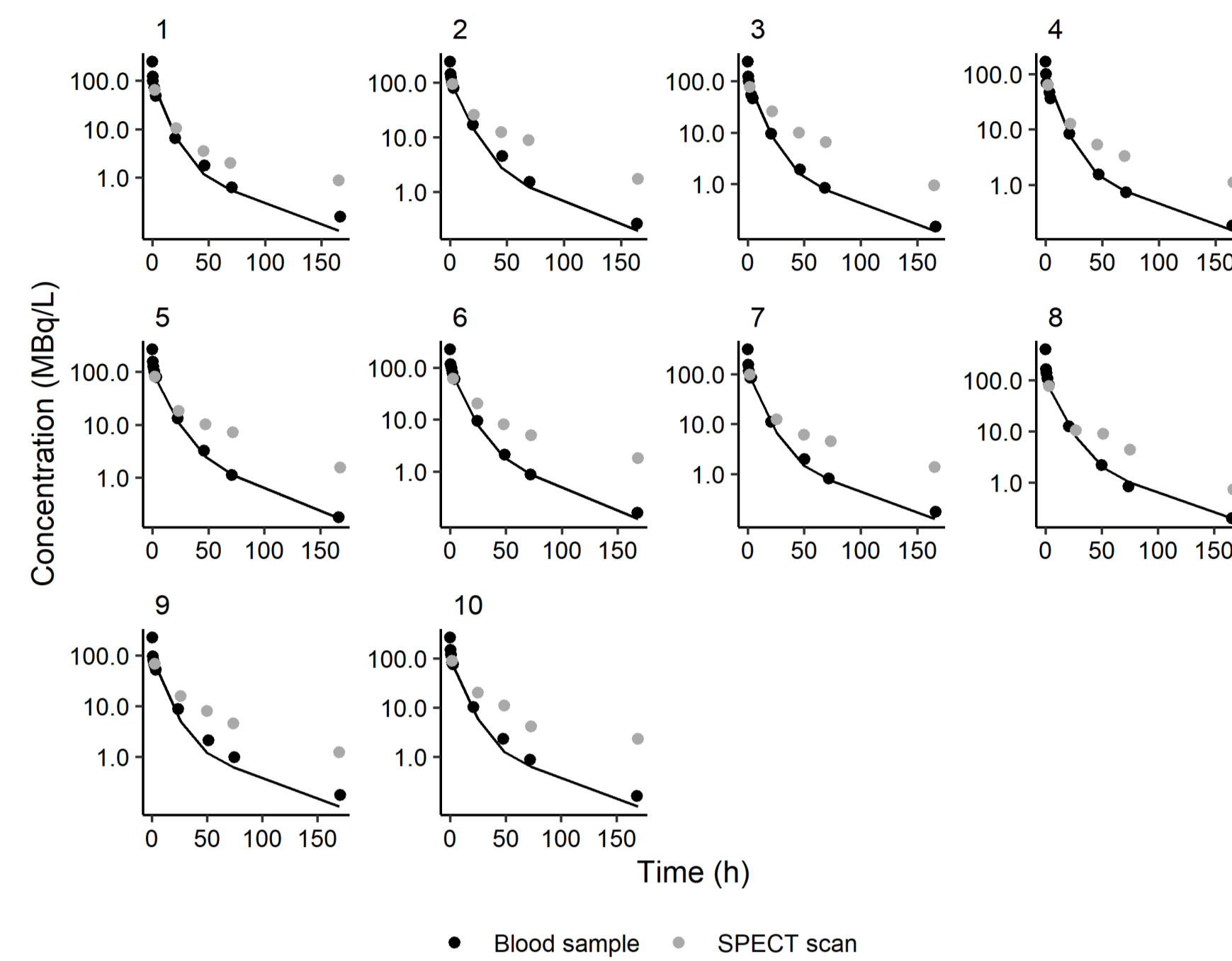


Fig 2. Individual blood concentration predictions (cycle 1) based on data derived from SPECT scans.

PARAMETER ESTIMATES

Parameter	Estimate (RSE%)
Structural parameters	
k ₁₀ (h ⁻¹)	0.290 (9.4)
k ₁₂ (h ⁻¹)	0.198 (53.5)
k ₂₁ (h ⁻¹)	0.14 (43.5)
k ₁₃ (h ⁻¹)	0.00872 (8.3)
k ₃₁ (h ⁻¹)	0.014 (2.5)
k ₁₄ (h ⁻¹)	0.0228 (6.6)
k ₄₁ (h ⁻¹)	0.0276 (4.9)
k ₁₅ (h ⁻¹)	0.000248 (23.0)
k ₅₁ (h ⁻¹)	0.00898 (9.0)
k ₁₆ (h ⁻¹)	1.06 (18.9)
k ₆₁ (h ⁻¹)	0.736 (15.6)
V1 (L)	10.3 (7.5)
Tumor volume on k ₁₅	0.703 (15.4)
BMAX2 (MBq) ¹	40.0 (12.8)
α (MBq/L) ²	6.27 (18.8)
β ²	0.828 (17.0)
γ (MBq/L) ³	0.273 (5.9)
IIV	
k ₁₀ (CV%)	17.3 (22.6)
k ₁₂ (CV%)	39.9 (22.4)
k ₁₃ (CV%)	16.6 (34.8)
k ₄₁ (CV%)	9.5 (34.7)
k ₁₅ (CV%)	59.2 (27.9)
BMAX2 (CV%)	47.2 (16.1)
IOV	
k ₁₅ (CV%)	43.2 (32.1)
RUV (proportional, CV%)	
Comp. 1 (blood samples)	19.0 (11.8)
Comp. 1 (SPECT data)	55.7 (12.6)
Comp. 2	19.4 (11.9)
Comp. 3	29.8 (9.9)
Comp. 4	87.1 (15.2)
Comp. 5	46.2 (11.4)
RUV (additive)	
Comp. 1 (MBq/L)	0.25

Eq 1. $dA/dt(2) = k_{12} * A1 * (1 - A2/BMAX2) - k_{21} * A2$

Eq 2. $C_{pred,ij} = C_{pred,SPECT,ij} * \beta + \alpha$

Eq 3. $C_{obs,ij} = C_{pred,ij} + \gamma$

RESULTS

- Six compartment model (see Fig. 1)
- Blood concentration predictions based on image-derived blood data were corrected to blood sample predictions (see Fig. 2 and Eq. 2)
- Liver concentrations were corrected for liver blood activity, because of its high vascularization
- Receptor saturation (BMAX) for salivary glands
- GFR as covariate on k₁₀ (linear function)
- Tumor volume as covariate on k₁₅ (power function)
- Interoccasion variability on k₁₅

CONCLUSION

- The final model adequately described ¹⁷⁷Lu-PSMA-617 uptake into relevant tissues in patients with low volume metastatic PCa
- IIV on PK parameters was rather small and IOV on the tumor uptake rate constant was estimated 43.2% (CV%)
- Using a population PK approach based on imaging data, it is possible to obtain information regarding population PK parameters and its variability within the population

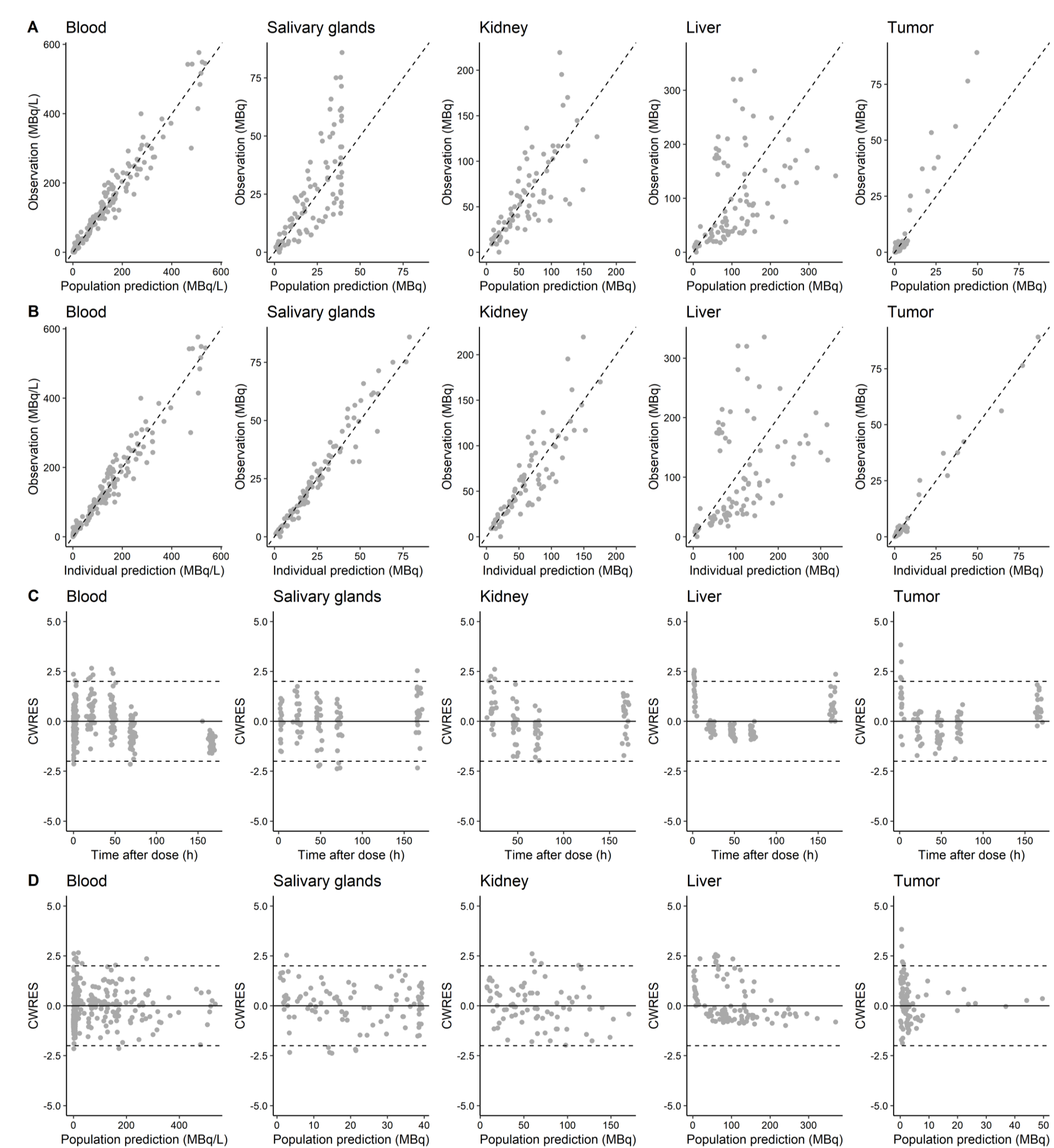


Fig 3. Goodness-of-fit plots of the final model for ¹⁷⁷Lu-PSMA-617, including population predictions (PRED) vs observations (A), individual predictions (IPRED) vs observations (B), conditional weighted residuals (CWRES) vs time after dose (C) and CWRES vs PRED (D), for all compartments separately.

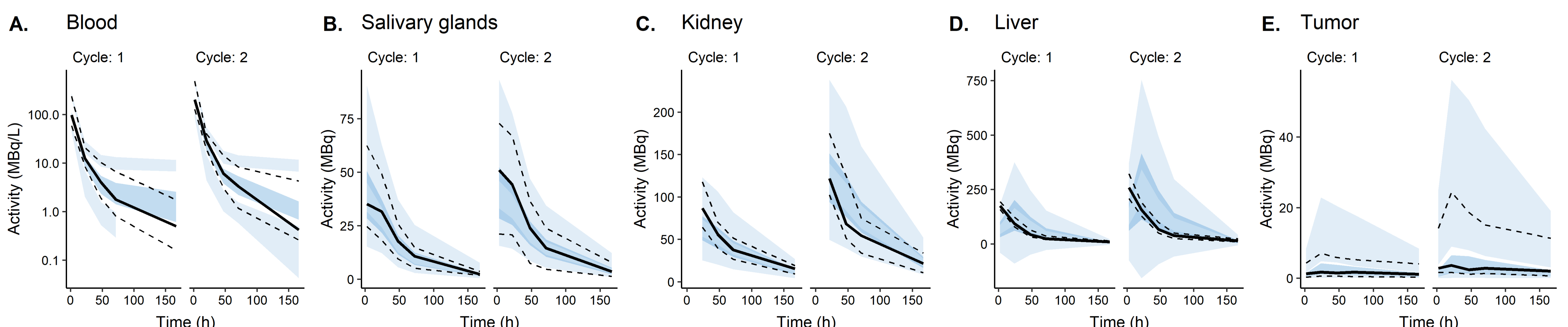


Fig 4. Visual predictive checks for each compartment, stratified per treatment cycle (1000 simulations). Solid lines and dashed lines represent median observed values and 5-95th percentiles of observed values, whereas dark and light blue areas represent 80% confidence intervals of the simulated median and 5-95th percentiles of simulated values.

REFERENCES

1. Sartor O et al. N Engl J Med. 2021;385(12):1091-103.
2. Prive BM, et al. Clin Cancer Res. 2021;27(13):3595-601