A Pre-Therapeutic Dose Prediction Workflow for Lu-177-PSMA Therapy: Integrating PBPK Modeling with Monte Carlo Simulation

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ABSTRACT

Purpose: To explore a comprehensive pre-therapeutic dose prediction workflow for Lu-177-PSMA radiopharmaceutical therapy by combining a physiologically based pharmacokinetic (PBPK) model with Monte Carlo simulation.

Methods: The PBPK model for Lu-177-PSMA was used to generate time-activity curves and time-integrated activities for major organs and tumor lesions. A virtual patient was configured with a tumor volume of 16.5 mL, a PSMA receptor density of 266 nmol/L, and an injected activity of 6.8 GBq. The PBPK model outputs were then converted into source terms and imported into the PHITS Monte Carlo simulation platform using the ICRP 110 adult male voxel phantom. The resulting organ absorbed doses were validated against IDAC calculations using the same TIA input.

Results: An integrated technical workflow combining the Lu-177-PSMA PBPK model with Monte Carlo dose calculation was successfully implemented, effectively bridging pharmacokinetic modeling and dose prediction. The PHITS-derived organ doses agreed closely with IDAC for the tumor and salivary glands, confirming the internal consistency of the workflow. Spatially resolved dose maps were obtained, showing a highly non-uniform dose distribution with the tumor dose substantially higher than that in surrounding normal tissue.

Conclusion: The established Lu-177-PSMA dose prediction workflow addresses a current gap in pre-therapeutic dose prediction and offers a reliable tool dose optimization. This systematic approach shows strong potential for clinical translation toward personalized, precise dosing in radiopharmaceutical therapy.

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INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, causing over 250,000 deaths annually. Many patients progress to metastatic castration-resistant prostate cancer (mCRPC), a highly aggressive and incurable stage.

Lu-177-PSMA therapy precisely targets PSMA-expressing lesions, with tumor absorbed doses exceeding organs at risk by a factor of 3–6. However, current clinical dosimetry relies on post-treatment SPECT/CT imaging—accurate but entirely retrospective. The field is therefore moving toward pre-therapeutic dose prediction using Physiologically Based Pharmacokinetic (PBPK) modeling. Yet current PBPK predictions stop at organ-level activity, leaving a missing link to spatially resolved dose distributions.

To address this gap, this study aimed to develop and evaluate a pre-therapeutic dose prediction workflow that connects PBPK-predicted biodistribution with Monte Carlo radiation transport, enabling spatially resolved dose maps before treatment.

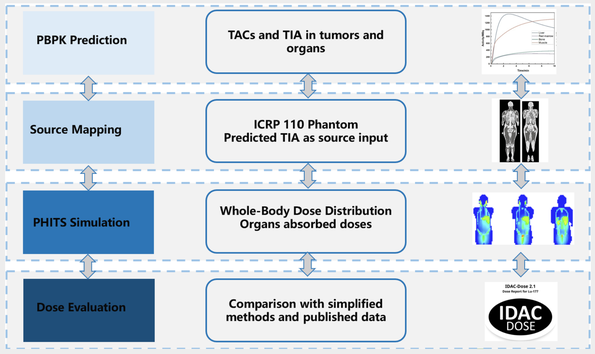

Figure 1. Integrated Workflow for Lu-177-PSMA Therapy Dose Prediction.

METHODS

The workflow consists of four main steps: (1) PBPK prediction to generate TACs and TIAs in tumors and organs; (2) source mapping to transfer the predicted TIAs into the ICRP 110 phantom; (3) PHITS Monte Carlo simulation to calculate whole-body dose distributions and organ absorbed doses; (4) dose evaluation by comparing results with IDAC. The aim is to support practical, mechanism-based, patient-specific pre-therapeutic dosimetry.

PBPK model: The Lu-177-PSMA PBPK model from Fele-Paranj et al. was implemented in MATLAB SimBiology. A virtual patient was configured with a tumor volume of 16.5 mL, a PSMA receptor density of 266 nmol/L, and an injected activity of 6.8 GBq. The model generated organ-level TACs and TIAs, which were normalized and mapped to the ICRP 110 adult male voxel phantom as source weights.

Monte Carlo simulation: PHITS was used with 10^7 particle histories, modeling beta and gamma emissions of ^{177}Lu. Dose maps were generated via an xyz mesh tally, and organ doses via a region-based tally. Results were validated against IDAC using the same TIA input.

RESULTS

The TACs captured the expected pharmacokinetic behavior of Lu-177-PSMA . Blood activity cleared rapidly within the first minutes, while the liver, spleen, and kidneys showed early uptake followed by gradual washout. In contrast, the tumor and salivary glands displayed a slower but sustained uptake.

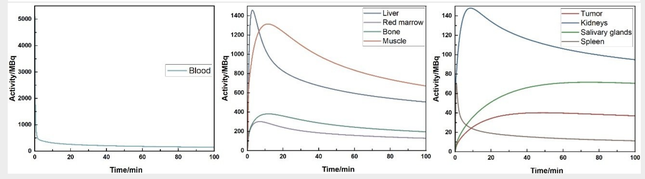

Figure 2. Time-activity curves (TACs) predicted by PBPK model from 0 to 100 min.

Integration of the TACs over 60,000 min yielded the TIAs. The liver had the highest TIA (8.40 GBq·h), followed by muscle (6.28 GBq·h) and kidneys (3.03 GBq·h). Tumor TIA was 1.80 GBq·h, comparable to salivary glands (1.90 GBq·h) and bone (1.83 GBq·h).

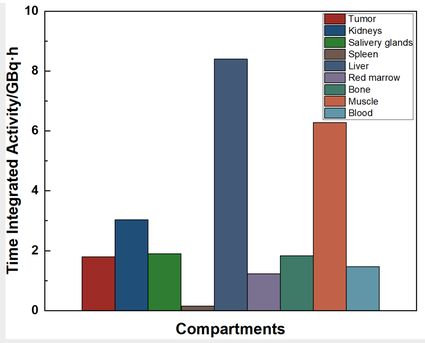

Figure 3. Time-integrated activity (TIA) predicted by PBPK model.

From the TIA values, PHITS generated spatially resolved dose. The dose distribution was highly non-uniform. And the tumor dose was substantially higher than in the surrounding normal tissue. Moving along the slices, the salivary glands faded, the tumor signal appeared and peaked, and then the kidneys emerged, confirming the correct anatomical placement of the sources.

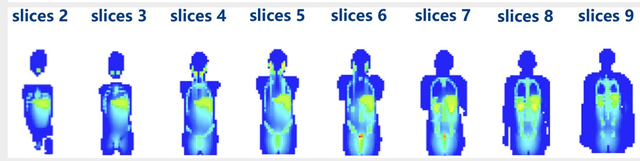

Figure 4. Spatially resolved dose maps (partial only).

The PHITS results agreed closely with IDAC for the tumor (2.4% difference) and salivary glands (3.4%), while the kidney difference was larger (25.1%).

Table 1. Comparison of normalized absorbed doses from PHITS and IDAC.

Tissue	PHITS (Gy/GBq)	IDAC (Gy/GBq)	Difference
Tumor	1.22	1.25	2.4%
Kidneys	0.115	0.0919	25.1%
Salivary glands	0.256	0.265	3.4%

DISCUSSION

The PBPK model accurately captured the expected pharmacokinetics of Lu-177-PSMA . Its mechanistic basis, which relies on physiologically meaningful parameters rather than purely data-driven correlations, provides a solid foundation for pre-therapeutic dose calculation.

The mapping of PBPK-predicted TIA values to the ICRP 110 phantom connected pharmacokinetic prediction with radiation transport simulation, and the resulting spatially resolved dose maps confirmed the correct anatomical placement of the sources.

The close agreement between PHITS and IDAC for the tumor and salivary glands demonstrates that the workflow produces internally consistent dose estimates. The larger difference observed for the kidneys reflects the different approaches of the two methods: IDAC relies on pre-computed S-values that assume standard organ geometries, whereas PHITS performs radiation transport directly in the voxelized anatomy. For an organ as large as the kidney, this difference has a greater impact on the calculated mean dose.

The workflow features a modular design: the PBPK model, the source mapping, and the dose calculation are kept as independent components. Each can be refined or replaced without rebuilding the entire chain. This modularity allows the framework to be extended to other radiopharmaceuticals, including α-emitters such as ^{211}At, and supports a progressive transition toward fully individualized pre-therapeutic dosimetry.

CONCLUSION

The established Lu-177-PSMA dose prediction workflow addresses a current gap in pre-therapeutic dose prediction by directly connecting PBPK modeling with Monte Carlo radiation transport.

This systematic approach offers a reliable tool for dose optimization and shows strong potential for clinical translation toward personalized, precise dosing in radiopharmaceutical therapy.

ACKNOWLEDGMENTS

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