Virtual Theranostic Trial (VTT) for Tracer-specific PSMA PET Imaging Protocol Optimization: Towards Reliable Digital-twin-based Predictive Dosimetry

Maziar Sabouri[1,2], James Fowler[1,2], Taylor J. McColl[2,3], Carlos F. Uribe[2,3,4], Arman Rahmim[1,2,3,4]

1 Department of Physics & Astronomy, University of British Columbia, Vancouver, BC, Canada | 2 Department of Basic and Translational Research, BC Cancer Research Institute, Vancouver, BC, Canada | 3 Department of Radiology, University of British Columbia, Vancouver, BC, Canada | 4 Department of Molecular Imaging and Therapy, BC Cancer, Vancouver, BC, Canada

2026 JULY 19–22 VANCOUVER, BC
JOINT AAPM | COMP MEETING

ABSTRACT

Introduction: Radiopharmaceutical therapy (RPT) with PSMA-targeting agents is traditionally delivered using fixed activity schemes, which fail to account for substantial inter-patient variability in radiopharmaceutical kinetics. We aimed to determine whether optimizing pre-therapy PSMA PET imaging protocols, incorporating dynamic and delayed acquisitions, enables more reliable prediction of ^{177}Lu-PSMA absorbed doses to support treatment personalization.

Methods: We conducted a 500-patient virtual theranostic trial (VTT) using a physiologically based pharmacokinetic (PBPK) model to evaluate three PSMA PET tracers (^{68}Ga, ^{18}F, ^{64}Cu). Protocols were optimized using covariance (COV) and Fisher Information Matrix (FIM D-/A-optimal) frameworks. We compared early dynamic-only protocols against "full" protocols augmented with a late static scan. Predictive performance was assessed via time-integrated activity (TIA) percentage errors across all modeled tissues.

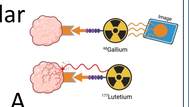
Results: Tracer performance, evaluated by combined absolute bias and inter-patient variability, followed the hierarchy ^{64}Cu > ^{18}F > ^{68}Ga. For both ^{64}Cu- and ^{18}F-PSMA, late-augmented full FIM-D protocols (e.g., 60-min dynamic + 11-min static) provided the most consistent dosimetry recovery, significantly reducing variance compared to dynamic-only designs. ^{64}Cu-PSMA demonstrated the highest overall accuracy. Conversely, for ^{68}Ga-PSMA, late statics yielded performance comparable to dynamic-only protocols, with no significant gains in accuracy.

Conclusion: This VTT demonstrates that tracer-specific, information-driven PET protocol optimization improves the reliability of digital twin-based predictive dosimetry. Protocols combining dynamic and delayed acquisitions, particularly for ^{64}Cu-PSMA under D-optimal sampling, outperformed dynamic-only approaches, providing a robust pathway toward personalized PSMA RPT.

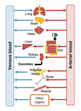
PyCNO

Introduction

- **Theranostics:** The approach of pairing diagnostic imaging agents with therapeutic counterparts to identify, treat, and monitor disease at the molecular level.



- **Radiopharmaceutical Therapy (RPT):** A systemic treatment using targeted radioligands to deliver ionizing radiation specifically to tumor sites while sparing healthy tissues.
- **Physiologically based pharmacokinetic (PBPK) Modeling:** A mathematical framework utilizing organ-specific physiological and kinetic parameters to predict the absorption, distribution, and excretion of therapeutic agents.



- **Virtual Theranostic Trials (VTT):** A computational platform using patient-specific data and kinetic modeling to simulate RPT outcomes, enabling non-invasive protocol optimization and dose prediction.

- **Current Limitations:** RPT is often delivered via fixed, "one-size-fits-all" schemes that neglect individual variability in radiopharmaceutical kinetics and organ uptake.

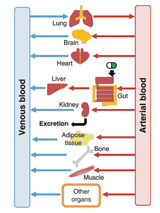
- **Clinical Need:** A requirement to leverage pre-therapy PSMA PET to reliably predict post-treatment dosimetry, enabling personalized treatment from the first cycle.
- **Study Objective:** To determine if optimizing pre-therapy PSMA PET protocols, specifically through dynamic and delayed acquisitions, enables more robust prediction of ^{177}Lu–PSMA absorbed doses.

Methods and Materials

1- Study Design: A 500-patient virtual theranostic trial (VTT) employing a physiologically based pharmacokinetic (PBPK) model with realistic noise.

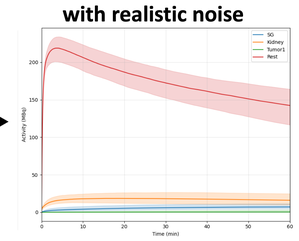
500-patient VTT

Physiologically based Pharmacokinetic (PBPK) Model



+ ^{68}Ga PSMA, ^{18}F PSMA, ^{64}Cu PSMA

Time activity curves (TACs) with realistic noise



2- Protocol Optimization: Compared early dynamic-only protocols (30–60 min, 1–300 s framing) against combined protocols including a late static scan (5–20 min, acquired 90 min to 1-week p.i.).

Early Dynamic PET 30-60 MIN

Phase 1 (0–2 min): $d_1 \in \{1, 3, 5, 10, 15, 20, 30\}$ s.

Phase 2 (2–10 min): $d_2 \in \{30, 45, 60\}$ s.

Phase 3 (10–30 min): $d_3 \in \{60, 90, 120\}$ s.

Phase 4 (30–T_{dyn} min): $d_4 \in \{120, 180, 240, 300\}$ s.

Late Static PET 5-20 MIN

Start times (t): 1.5 h to 168 h.

Durations (Δt_d): {5, 6, … , 19, 20} minutes.

3- Optimization Framework: Utilized covariance (COV) and Fisher Information Matrix (FIM D-/A-optimal) methods for protocol refinement.

Coefficient Of Variation (COV)

- An approach used to identify imaging windows where patients exhibit the greatest inter-subject variability in kinetic profiles.

Fisher Information Matrix (FIM)

- The Fisher Information Matrix (FIM) quantifies the information content that an imaging protocol provides about the parameters of interest. By analyzing the FIM, we optimize acquisition settings to maximize parameter precision while minimizing uncertainty.

$$D_i(t, \Delta t_d) = \frac{\bar{\sigma}_i(t, \Delta t_d)}{\sigma_{\text{noise},i}(t, \Delta t_d)} = \frac{\bar{\sigma}_i(t, \Delta t_d)}{\alpha \sqrt{\bar{\mu}_i(t, \Delta t_d) \cdot T_{\text{ref}} / \Delta t_d}}$$

FIM-D $\Phi_D(\mathbf{F}) = \log\det(\mathbf{F})$ & FIM-A $\Phi_A(\mathbf{F}) = \mathrm{tr}(\mathbf{F}^{-1})$

4- Kinetic Modeling: Estimated ten pharmacokinetic parameters via a Cluster Gauss–Newton framework

Cluster Gauss-Newton

Pharmacokinetics

Parameter	Units	Physical Meaning	Organ
$R_{\text{den}}^{\text{SG}}$	nmol/L	Receptor density	SG
$R_{\text{den}}^{\text{Kid}}$	nmol/L	Receptor density	Kidney
$R_{\text{den}}^{\text{Tum}}$	nmol/L	Receptor density	Tumor
$\lambda_{\text{Rel}}^{\text{SG}}$	min^{-1}	Release rate	SG
$\lambda_{\text{Rel}}^{\text{Kid}}$	min^{-1}	Release rate	Kidney
$\lambda_{\text{Rel}}^{\text{Tum}}$	min^{-1}	Release rate	Tumor
f_{SG}	mL/min/g	Perfusion	SG
f_{Kid}	mL/min/g	Perfusion	Kidney
f_{Tum}	mL/min/g	Perfusion	Tumor
f_{exc}	(fraction)	Excretion fraction	kidney

Time Integrated Activity % errors

Results

Overall Hierarchy: ^{64}Cu- > ^{18}F- > ^{68}Ga-PSMA

Optimal Strategy: Late-augmented full FIM-D (dynamic + static) consistently outperforms dynamic-only protocols.

Top Performer: ^{64}Cu-PSMA provides the highest overall dosimetry accuracy and consistency.

^{64}Cu-PSMA

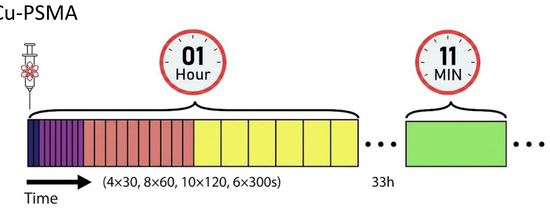


Figure: Optimized ^{64}Cu-PSMA acquisition protocol yielding the highest dosimetry accuracy. The protocol comprises an early dynamic acquisition phase (4 × 30 s, 8 × 1 min, 10 × 2 min, 6 × 5 min) followed by an 11-min late static scan.

Table: Dosimetry recovery errors by protocol and isotope.

Isotope	Protocol	SG	Kidney	Tumor1	Rest
^{68}Ga-PSMA	COV · dyn-only	1.18 ± 6.13	0.49 ± 7.48	−1.09 ± 18.24	0.00 ± 0.33
	FIM-D · dyn-only	1.21 ± 6.38	0.46 ± 7.38	−0.82 ± 18.49	0.01 ± 0.45
	FIM-A · dyn-only	1.73 ± 10.63	0.36 ± 9.33	−0.83 ± 19.08	−0.19 ± 3.23
	COV · full	1.29 ± 6.45	0.69 ± 8.32	−1.76 ± 17.24	0.03 ± 0.89
	FIM-D · full	1.09 ± 6.99	0.30 ± 7.38	−1.84 ± 17.52	−0.02 ± 0.70
	FIM-A · full	1.18 ± 13.90	−0.15 ± 9.99	−5.15 ± 24.71	−1.11 ± 5.91
^{18}F-PSMA	COV · dyn-only	1.12 ± 6.60	0.43 ± 7.63	−0.86 ± 18.45	−0.04 ± 1.09
	FIM-D · dyn-only	1.37 ± 6.61	0.71 ± 8.01	−1.15 ± 18.41	−0.02 ± 0.91
	FIM-A · dyn-only	1.84 ± 12.77	0.81 ± 8.34	−1.52 ± 18.64	−0.00 ± 2.71
	COV · full	1.40 ± 6.58	0.70 ± 7.67	−2.10 ± 16.45	0.01 ± 1.14
	FIM-D · full	1.56 ± 6.01	0.51 ± 7.38	−1.87 ± 15.65	0.03 ± 0.20
	FIM-A · full	1.43 ± 7.75	0.58 ± 7.94	−2.41 ± 16.86	0.02 ± 1.16
^{64}Cu-PSMA	COV · dyn-only	1.64 ± 6.50	0.91 ± 7.68	−1.24 ± 18.02	−0.00 ± 0.94
	FIM-D · dyn-only	1.30 ± 7.64	1.00 ± 8.12	−1.40 ± 18.54	−0.19 ± 2.57
	FIM-A · dyn-only	1.43 ± 6.78	0.86 ± 7.91	−1.10 ± 17.67	−0.03 ± 1.83
	COV · full	1.76 ± 8.50	1.01 ± 7.72	−3.25 ± 13.74	−0.01 ± 0.64
	FIM-D · full	**0.20 ± 3.82**	**0.05 ± 3.38**	**−1.84 ± 10.81**	**−0.00 ± 1.71**
	FIM-A · full	1.58 ± 5.93	0.58 ± 4.72	−3.53 ± 12.56	−0.03 ± 1.01

Conclusions

Superiority: Dynamic + delayed protocols outperform dynamic-only capturing patient-specific kinetics.

Best Tracer: ^{64}Cu-PSMA showed the strongest performance under D-optimal sampling.

Impact: Information-driven protocols enable practical, personalized radiopharmaceutical therapy.