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

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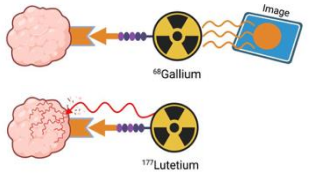
Introduction

PSMA-targeted radiopharmaceutical therapy (RPT) currently involves **fixed, one-size-fits-all dosing.**

This ignores significant **inter-patient variability** in kinetics and organ uptake.

Gap:
Can Pre-therapy PSMA PET reliably predict therapy doses towards precision therapies?

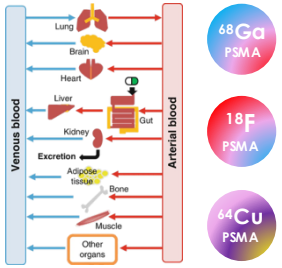


AIM: Determine if **optimized PSMA PET protocols** (dynamic + delayed scans) improve **^{177}Lu-PSMA dose predictions.**

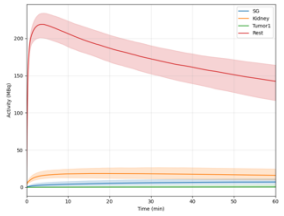
Methods

500-patient VTT

Physiologically based Pharmacokinetic (PBPK) Model



Time activity curves (TACs) with realistic noise



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): $d_4 \in \{180, 240, 300\}$ s.

Late Static PET 5-20 MIN

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

Durations (Δt_d): {30, 35, 40, 45, 50, 55, 60} minutes.

Coefficient Of Variance (COV)

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

Fisher Information Matrix (FIM)

$$\Phi_D(\mathbf{F}) = \log\det(\mathbf{F})$$

$$\Phi_A(\mathbf{F}) = \mathrm{tr}(\mathbf{F}^{-1})$$

Cluster Gauss-Newton

Parameter	Units	Physical Meaning
$R_{\text{den}}^{\text{SG}}$	nmol/L	Receptor density, salivary gland
$R_{\text{den}}^{\text{Kid}}$	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, salivary gland
f_{Kid}	mL/min/g	Perfusion, kidney
f_{Tum}	mL/min/g	Perfusion, tumor
f_{exc}	(fraction)	Excretion fraction, kidney

Pharmacokinetics

Time Integrated Activity % errors

Results

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

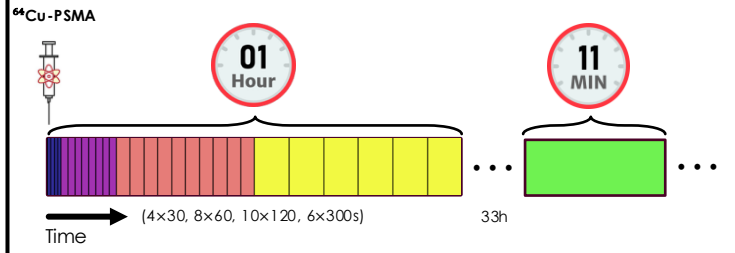


Table: Dosimetry recovery errors by protocol and isotope.

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

Conclusion

Reliability: Optimized PSMA PET protocol improves digital twin ^{177}Lu-PSMA dose predictions.

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

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

Impact: Information-driven protocols enable practical, personalized RPT.