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PHYSICS CONTRIBUTION

Machine Learning-based Dose Prediction in [¹⁷⁷Lu]Lu-PSMA-617 Therapy by Integrating Biomarkers and Radiomic Features from [⁶⁸Ga]Ga-PSMA-11 Positron Emission Tomography/Computed Tomography

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Purpose: The study aimed to develop machine learning (ML) models for pretherapy prediction of absorbed doses (ADs) in kidneys and tumoral lesions for patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing [¹⁷⁷Lu]Lu-PSMA-617 (Lu-PSMA) radioligand therapy (RLT). By leveraging radiomic features (RFs) from [⁶⁸Ga]Ga-PSMA-11 (Ga-PSMA) positron emission tomography/computed tomography (PET/CT) scans and clinical biomarkers (CBs), the approach has the potential to improve patient selection and tailor dosimetry-guided therapy.

Methods and Materials: Twenty patients with mCRPC underwent Ga-PSMA PET/CT scans before the administration of an initial 6.8 ± 0.4 GBq activity of the first Lu-PSMA RLT cycle. Posttherapy dosimetry involved sequential scintigraphy imaging at ~4, 48, and 72 hours, along with a single photon emission computed tomography (SPECT)/CT image at around 48 hours, to calculate time-integrated activity coefficients. Monte Carlo (MC) simulations, leveraging the Geant4 application for tomographic emission toolkit, were employed to derive ADs. The ML models were trained using pretherapy RFs from Ga-PSMA PET/CT and CBs as input, whereas the ADs in kidneys and lesions (n = 130), determined using MC simulations from scintigraphy and SPECT imaging, served as the ground truth. Model performance was assessed through leave-one-out cross-validation, with evaluation metrics including R^2 and root mean squared error (RMSE).

Results: The mean delivered ADs were 0.88 ± 0.34 Gy/GBq for kidneys and 2.36 ± 2.10 Gy/GBq for lesions. Combining CBs with the best RFs produced optimal results: the extra trees regressor was the best ML model for predicting kidney ADs, achiev-

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0360-3016/\$ - see front matter © 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies. https://doi.org/10.1016/j.ijrobp.2025.05.014 ing an RMSE of 0.11 Gy/GBq and an R^2 of 0.87. For lesion ADs, the gradient-boosting regressor performed best, with an RMSE of 1.04 Gy/GBq and an R^2 of 0.77.

Conclusions: Integrating pretherapy Ga-PSMA PET/CT RFs with CBs shows potential in predicting ADs in RLT. To personalize treatment planning and enhance patient stratification, it is crucial to validate these preliminary findings with a larger sample size and an independent cohort. © 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed noncutaneous malignancy in men.¹ Androgen deprivation therapy (ADT) has long been the cornerstone of PCa treatment.² However, most PCa tumors eventually become resistant to ADT, leading to nonmetastatic or metastatic castration-resistant prostate cancer (nm/mCRPC).³ The latter, mCRPC, represents the most aggressive and lethal form of the disease.⁴

Prostate-specific membrane antigen (PSMA) is a glycoprotein that is overexpressed in malignant prostate cells while showing minimal expression in benign or nonprostatic tissues. This selective expression makes PSMA an ideal target for both the precise diagnosis and targeted treatment of PCa.⁵ [⁶⁸Ga]Ga-PSMA-11 (Ga-PSMA) PET/CT imaging has revolutionized the detection of cancer lesions in mCRPC, enabling the identification of patients who may benefit from [¹⁷⁷Lu] Lu-PSMA-617 (Lu-PSMA) radioligand therapy (RLT).⁶

Despite promising results, RLT raises concerns regarding balancing therapeutic benefits and potential side effects.⁷ The prevailing "one-dose-fits-all" approach may result in under- and overtreatment.⁸ Therefore, personalized RLT, guided by optimal radiation doses, is needed, similar to external radiation therapy and brachytherapy.⁹ Although quantitative imaging-driven Monte Carlo (MC) simulation methods are the gold standard for personalized dosimetry, their extensive requirements, such as the significant computational power and time needed to perform these simulations, make them impractical for routine clinical practice.¹⁰

Although there are many studies in radiopharmaceutical therapies (RPTs) focusing on internal dosimetry after the first therapy cycle to inform subsequent cycles, pretherapy predictions offer distinct advantages.¹¹⁻¹³ A fundamental aspect of treatment planning in RLT is estimating the absorbed doses (ADs) in both tumoral lesions and organs at risk (OARs) prior to therapy, which can potentially mitigate risks associated with treatment-induced toxicities.¹⁴ Pretherapy imaging provides crucial insights into the biodistribution of the therapeutic agent, facilitating tailored and safe dose adjustments for individual patients.^{15,16} Previous studies have investigated various applications of pretherapy PET metrics in RPTs.^{17,18} Among these, some have focused on predicting ADs using PET metrics, particularly in OARs and mainly in patients with neuroendocrine tumor (NET), with a few studies also incorporating clinical biomarkers (CBs) to improve predictive accuracy.^{17,19-21}

Data-driven machine learning (ML) algorithms, capable of recognizing complex patterns and accounting for

multivariate correlations, outperform simple linear regression by reducing uncertainties and significantly improving predictive accuracy.^{19,21} Peterson et al²² developed predictive models for kidney AD in NETs treated with [¹⁷⁷Lu]Lu-DOTA-TATE. Using pretherapy PET-standardized uptake value (SUV) metrics and estimated glomerular filtration rate (eGFR) biomarkers, their model achieved about 18% accuracy in estimating posttherapy renal AD. They further explored the predictive power of Ga-PET SUV metrics combined with baseline biomarkers to develop ML models for tumor AD prediction.²³ Radiomics in medical imaging offers the advantage of extracting imperceptible data, inaccessible through the naked eye, thus enhancing noninvasive analysis.^{17,24-26} Plachouris et al²¹ developed a pretreatment planning model for predicting ADs in OARs of patients with NET undergoing [177Lu]Lu-DOTA-TATE, leveraging ML algorithms. Their approach combined radiomic and dosiomic features, showing promising results for personalized OAR AD prediction.

Xue et al^{19⁷} used ML models to predict AD in OARs during [¹⁷⁷Lu]Lu-PSMA I&T RLT, using first-order features from Ga-PSMA PET imaging and laboratory measurements. A recent study has also shown promising results in predicting ADs of OARs in patients with NET using radiomic features (RFs) and ML algorithms.²¹ Besides the dosimetry of OAR, the evolving oncology landscape emphasizes tumor textural analysis, which measures spatial heterogeneity.²⁵ In this context, estimating the tumor AD before initiating the RLT could provide a quantitative measure for dose prediction, potentially enhancing patient-treatment outcomes.

Given the paucity of studies on pretherapy predictions of kidney and tumoral lesion ADs in Lu-PSMA RLT for patients with mCRPC, this study aimed to address this gap and use MC patient-specific dosimetry as a reference to develop ML regression models. These models incorporate RFs from Ga-PSMA PET/CT scans with baseline CBs. We hypothesized that including CBs in our models could better account for patient-specific kinetics that impact ADs, which are challenging to extract from imaging a short-lived surrogate, thereby enhancing predictive accuracy beyond Ga-PSMA PET uptake alone. This approach can potentially streamline the dosimetry workflow by reducing the necessity for multiple imaging sessions with prolonged procedures. Furthermore, identifying these predictive features provides valuable insights for clinical decision-making, particularly in addressing dosimetry-guided treatment planning in RLT.

Methods and Materials

Patient population and CBs

Twenty patients (68.28 \pm 6.44 year), with histopathologically proven PCa participated in this study. Inclusion criteria were mCRPC with PSMA-expressing lesions visible on Ga-PSMA PET/CT imaging within 2 months of treatment. These patients then received the initial cycle of Lu-PSMA RLT as part of their standard treatment protocol. As part of an institutional review board-approved ongoing research study, all patients provided written informed consent to participate in the dosimetry investigation.

The cohort's accurate net administered dose of RLT, averaging 6.8 ± 0.4 GBq, was determined by subtracting any residual activity in the syringe from the original assayed value. Patients underwent 3 scintigraphy imaging and a single photon emission computed tomography/computed tomography (SPECT/CT) session around 48 hours postinjection. Blood tests were collected 1 to 7 days before the RLT cycle and provided CBs.

The clinical variable set, detailed in Table 1, includes 3 demographic variables, 1 treatment history variable, 9 blood biomarkers, and 1 histopathology biomarker. This set was determined in collaboration with our nuclear medicine clinicians, who identified these factors as crucial for patients with mCRPC undergoing Lu-PSMA therapy. Including these variables enhances our understanding of factors affecting patient dose prediction, consistent with recent

studies highlighting their relevance in this population.^{19,27}

[⁶⁸Ga]Ga-PSMA-11 PET/CT Imaging

Patients underwent pretherapy Ga-PSMA imaging on a Siemens Biograph 6 TruePoint scanner, with an average activity of 148 \pm 16.92 MBq. Scans were performed 2 days to 2 months before treatment, and RLT eligibility was assessed. Whole-body PET scans from the vertex to the mid-thighs were acquired in 3-dimensional (3D) mode, with 3 to 4 minutes per bed position. Imaging initiated 45 to 60 minutes postinjection and used an ordered-subset expectation maximization (OSEM) iterative algorithm, with a 168 × 168 matrix size and 4.072 mm pixel size. A low-dose CT scan was also acquired for attenuation correction with a 512 × 512 matrix size, 0.97 mm pixel size, 110 kV_p, 80 mA, 3 mm slice thickness, and a pitch of 1.5.

[¹⁷⁷Lu]Lu-PSMA-617 Scintigraphy and SPECT/CT imaging

For patient-specific MC dosimetry in Lu-PSMA RLT, serial posttherapy scintigraphy was conducted at \sim 4, 48, and 72 hours following the initial RLT cycle and a quantitative SPECT/CT scan at around 48 hours. SPECT scans were acquired using a dual-headed Siemens Symbia T₂ system equipped with a low-energy high-resolution (LEHR)

Variable type	Variable name	Variable definition	Mean (range)				
Morphological	Age (y)	Patient's age (y)	69.52 (54-89)				
	Weight (kg)	Patient's weight (kg)	89.75 (70-155)				
	Height (cm)	Patient's height (cm)	172.06 (168-180)				
Historical	Previous therapies (n)	The number of therapies before RLT, including prostatectomy, EBRT, chemotherapy, and ADT	2.07 (1-3)				
Blood tests	PSA (μg/L)	Serum prostate-specific antigen, a glycoprotein enzyme (milligrams per deciliter)	59.01 (1.18-559.8)				
	CR (mg/dL)	Creatinine (mg/dL): a waste product, removed from the blood through the kidneys	0.97 (0.8-1.2)				
	ALP (U/L)	Alkaline phosphatase (U/L): an enzyme that is produced by several cells including osteoblasts (eg, increase in osteoblastic metastasis)	187.79 (93-384)				
	WBC (× $10^3/\mu$ L)	White blood cell count (× $10^3/\mu$ L)	6.49 (4.9-10.43)				
	RBC (×10 ⁶ /L)	Red blood cell count ($\times 10^6$ / L)	4.28 (3.53-5.93)				
	HB (g/dL)	Hemoglobin (g/dL): a protein in RBCs that carries oxygen	12.04 (10-14.9)				
	HCT (%)	Hematocrit (%): the percentage by volume of RBCs in the blood	35.79 (14-42.5)				
	K (mEq/L)	Serum potassium (milli-equivalents per liter)	3.83 (2.83-4.85)				
	Ca (mg/dL)	Serum Calcium	9.48 (9.2-10.1)				
Histopathology	GS	Gleason score: a grading system for PCa. Gleason scores range from 6 (low-grade cancer) to 10 (high-grade cancer)	Mode: 8 (7-10)				
Abbreviations: ADT = androgen deprivation therapy: EBRT = external beam radiotherapy: mCRPC = metastatic castration-resistant prostate cancer:							

 Table 1
 Clinical variables of 20 patients with mCRPC in the study

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; mCRPC = metastatic castration-resistant prostate cancer; PCa = prostate cancer; RBC = red blood cell; RLT = radioligand therapy; WBC = white blood cell.

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collimator. According to MIRD Pamphlet No. 26, a single 20% energy window centered on the lower 113-keV photopeak is preferable when using a low-energy collimator, such as LEHR, to optimize image quality.²⁸

In a single-bed configuration with autocontouring, both kidneys and most lesions, which were predominantly located in the pelvic region, were covered. However, this setup excluded the liver and spleen. A 2-bed configuration was used in a few cases with widespread metastasis to the abdominal and pelvic regions when the SPECT/CT system was available for research. Prioritizing the kidneys and lesions was essential as each mCRPC patient has 2 kidneys and multiple lesions, providing more data points to strengthen the modeling. Covering additional OARs, such as the salivary glands, liver, and spleen, required a 2- or 3-bed configuration, but this was not feasible because of scanner availability constraints.

Images were reconstructed using the OSEM iterative technique, with 8 iterations and 8 subsets. Attenuation corrections were applied using low-dose CT scans, followed by a post-reconstruction Gaussian filter of 5 mm full-width half-maximum, achieving an isotropic resolution of 4.79 mm. Scintigraphy and SPECT/CT scan parameters are detailed in Table 2.^{13,28}

Tumoral lesion and kidney segmentation

In contrast to semiautomated methods that rely on fixed thresholds (eg, 50% or 20% of maximum uptake), a board-certified nuclear medicine physician visually assessed tracer uptake and manually delineated the kidneys and lesions using the "Segment Editor" module of 3D Slicer software v5.2.2. We focused our analysis on the largest 8 lesions per patient, deliberately excluding those <4 mL (2 cm) [4]. This decision was made to enhance the reliability of our findings by reducing the potential impact of partial volume effect (PVE) on smaller lesions. Furthermore, we performed manual segmentation on the higher-resolution PET/CT images

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slice-by-slice. These segmentations were then coregistered onto the corresponding SPECT/CT images, and regions were carefully adjusted to ensure accuracy, a time-consuming task. Additionally, we included only lesions that were visible in planar images for time-integrated activity (TIA) calculations. This approach not only minimized the impact of PVE but also preserved the clinical relevance of our study.

Tumoral lesions were categorized as bone metastases (BM), lymph node metastases (LNM), and soft tissue (ST), each with distinct labels, with the prostate bed considered as ST. The true position of the kidneys was determined on CT slices, including the medulla and cortex, while excluding the vessels, cysts, renal pelvis, and adjacent structures. Kidneys and tumoral lesions were included based on anatomical size and distinct margins. Segmentations were validated and adjusted by a second experienced nuclear medicine physician. Figure 1 shows the manual segmentation of 3 patients with mCRPC in PET/CT and SPECT/CT images, highlighting left and right kidneys (LK and RK), BM, LNM, and ST in transaxial views.

Hybrid dosimetry workflow

Figure 2 illustrates the hybrid dosimetry workflow, followed by a detailed breakdown of each step. After preparing Lu-PSMA, the injection time was recorded and the initial and remaining syringe activity was measured to determine the net activity administered. Patients underwent scintigraphy imaging at approximately 4, 48, and 72 hours postinjection, with SPECT/CT imaging at approximately 48 hours for precise tracking of the radiopharmaceutical's temporal distribution.

Partial-volume correction (PVC) was not applied in this study for several reasons. One primary reason is the lack of a universally accepted method for PVC at the organ or voxel level.²⁹ A common approach at the organ or tumor level involves using volume-dependent recovery coefficients

Table 2	SPECT/CT	and whole-body	' planar	' imaging	acquisition	parameters
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Whole-body planar acquisition		SPECT acquisition		CT acquisition				
Parameter	Value	Parameter	Value	Parameter	Value			
Matrix size	1024×256	Matrix size	128×128	Matrix size	512 × 512			
Pixel size	2.4 mm × 2.4 mm	Voxel size	4.8 mm × 4.8 mm × 4.8 mm	Voxel size	0.97 mm × 0.97 mm × 5 mm			
Scan time	∼15 min (depending on patient's height)	Scan time (frame duration (s/fr) and projections)	~24 min (20 fr/s, 64 projections per head)	Scan time	$\sim 1 \min$			
Energy window	Center: 113, 15% photopeak, 10% lower and upper scatter.	Collimator	LEHR, 113 keV	Tube voltage, current, and pitch	110 kV, 55 mAs, and 1.5			
Abbreviations: $CT = computed tomography: LEHR = low-energy high-resolution: SPECT = single photon emission computed tomography.$								



Fig. 1. Manual segmentation of targets in PET/CT and SPECT/CT images for 3 patients with mCRPC, with detailed delineation of bone metastases (BM), lymph node metastases (LNM), and soft tissue (ST) lesions, along with the right and left kidneys (RK and LK), depicted on transaxial views. *Abbreviations:* CT = computed tomography; LK = left kidney; mCRPC = metastatic castration-resistant prostate cancer; PET = positron emission tomography; RK = right kidney; SPECT = single photon emission computed tomography.

obtained from phantom measurements, such as those using spherical inserts of varying sizes. However, this method has well-known limitations, as recovery coefficients are influenced by factors such as volume, activity distribution, and shape.²⁹⁻³² Given these limitations, we chose not to employ phantom-based PVE corrections and treated PVC as part of the image segmentation step of dosimetry, which was described in the previous section.^{29,33}

A calibration technique was employed to derive a SPECT camera calibration factor (cps/MBq) from the ratio of total counts in the reconstructed image to scan duration multiplied by net activity. This factor converted SPECT images from counts to Becquerel (Bq) units.^{28,34-36}

SPECT/CT images underwent segmentation (as described previously) to extract activity within each volume of interest (VOIs), including kidneys and lesions. Scintigraphy images were coregistered using 3-D Slicer software, with regions of interest (ROIs) delineated on the 4 hours anterior scan. To ensure consistency in contouring and quantification, the initial ROIs were maintained in size and shape and manually repositioned on subsequent anterior views, with a 180° reversal applied to posterior views. Scintigraphy activities were quantified using the conjugate view method to obtain a 2D-based time-activity curve (TAC), which was then rescaled using quantitative SPECT data (as indicated by the star in the TAC of Fig. 2a).^{37,38}

To understand the kinetic of the radiopharmaceutical, rescaled TACs with uniformly weighted activities were integrated using a triple-exponential equation to obtain TIA coefficient or $\sim A$ values, representing total disintegrations in each VOI.³⁹

CT images were resampled using Lanczos interpolation with the "Resize Image (BRAINS)" module in 3D Slicer to match SPECT/CT resolution and dimensions (Fig. 2b). Hounsfield units (HUs) were transformed into materials and densities using the Schneider tables.²⁸ The activity and density maps (from SPECT/CT) were input into the Geant4 application for tomographic emission (GATE) simulation platform (v9.2, using Geant4 v11.0) to obtain the absorbeddose-rate map (ADRM), the rate at which energy is deposited by radiation in a given tissue or volume per unit time (Gy/s).⁴⁰

GATE includes a feature called DoseActor, which records the AD within a specified volume as a 3D matrix.⁴⁰ The GATE MC simulation used the MersenneTwister random seed and included processes from both the electromagnetic emstandard opt3 and RadioactiveDecay physics lists. With 10⁹ primaries, the simulation achieved a mean statistical uncertainty of about 3%. The mean absorbed-dose rate was determined by applying the mask of VOIs in the voxelized absorbed-dose-rate maps. In the final stage (Fig. 2c), the mean AD for each VOI was determined through the analytical multiplication of the absorbed-dose-rate mean and region-based TIA coefficients, which were obtained from the estimated activity concentration over time.¹³ ADs were computed in both Gy and Gy/GBq (per administered activity) for VOIs. ADs per administered activity (Gy/GBq) served as the target for ML algorithms.

Radiomics workflow

Figure 3 illustrates the radiomics workflow, outlining the following steps: data collection (PET/CT images, patient characteristics, and laboratory data), PET/CT VOI segmentation, preprocessing, feature extraction, feature selection, model construction, and model evaluation. The imaging protocol, CBs, and segmentation have been described in

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Fig. 2. Hybrid dosimetry workflow in this study. (a) Net activity measurement, scintigraphy and SPECT/CT imaging, calibration, registration, segmentation, plotting time-activity curves (TACs), and calculating time-integrated activities (TIAs). (b) Image preprocessing, Monte Carlo simulation, and absorbed-dose-rate mean calculation. (c) Final dose calculation. *Abbrevia-tions:* CT = computed tomography; SPECT = single photon emission computed tomography.

previous sections. This section elaborates on feature extraction through model evaluation.

Radiomics feature extraction

Following the manual segmentation, image preprocessing and feature extraction were conducted using the LIFEx package v7.4.0.^{41,42} Preprocessing encompassed spatial resampling to $3 \times 3 \times 3$ mm³, intensity discretization, and intensity rescaling, with consistent settings applied across all patients. PET images were discretized into 64 gray levels using absolute intensity rescaling, with intensity values ranging from 0 to 139 (the maximum SUV in the data set). CT images were discretized into 10 bins using absolute intensity rescaling, with HUs ranging from -1000 to 3000.

A total of 243 RFs were extracted from each VOI, comprising 124 PET RFs and 119 CT RFs. These features were categorized into first-order and second-order features. First-order features were further categorized into morphological, intensity-based, and intensity-histogram features. Morphologic features quantify the 3D shape and size of the VOIs, encompassing parameters such as volume size and



Fig. 3. Radiomics workflow applied in this study. The workflow includes data collection (PET/CT images, patient characteristics, lab data), VOI segmentation, image preprocessing (spatial resampling, intensity discretization, rescaling), feature extraction (shape, intensity, texture), feature selection (LASSO with *q*-value correction), model construction (machine learning with LOOCV), and model evaluation (predictive performance and correlation analysis). *Abbreviations:* CT = computed tomography; LASSO = least absolute shrinkage and selection operator; LOOCV = leave-one-out cross-validation; PET = positron emission tomography; VOI = volume of interest.

surface area. Tumor lesion location was included as a "LOC" feature, categorizing BM as 1, LNM as 2, and ST as 3.

Intensity-based features were derived from the intensity values, encompassing features such as minimum, mean, and skewness. Intensity-histogram features are statistical features derived from histograms of the intensity values. Second-order features, or textural features, are computed based on the spatial relationships between voxels. These features are further categorized into graylevel co-occurrence matrix (GLCM), gray-level run length matrix, neighboring gray-tone difference matrix (NGTDM), and gray-level size zone matrix (GLSZM) features.

Radiomics feature selection

Radiomics processing and ML pipeline were conducted in Python V.3.11.5. Features were *z*-score normalized before selection, ensuring zero mean and unit variance.

Overfitting poses a significant concern in ML investigations, particularly when the feature count exceeds the sample size. To address this, the least absolute shrinkage and selection operator was used to select the most informative predictive features. Seven-fold cross-validation was applied to determine the optimal tuning parameter. Subsequently, Pearson coefficient of correlation and Spearman's rank correlations were analyzed between predictive features and ADs of kidneys and lesions, respectively, followed by Benjamini and Hochberg *P*value correction, considering *Q*value < .05 as significant.

ML construction

Multiple linear and nonlinear ML regression algorithms were employed, including linear regression, ElasticNet regression, random forest regressor, gradient-boosting regressor (GBR), eXtreme gradient boosting, extra trees regressor (ETR), support vector regression, decision tree regression, K neighbors regressor, and adaptive boosting (AdaBoost) regression to determine the optimal regression algorithm.

Experiments

The study comprised a series of experiments investigating the predictive power of various feature categories, including PET RFs, CT RFs, and CBs in predicting mean ADs. These experiments were integrated into the ML models, evaluating their performance separately for kidneys and lesions. Experiments 1 to 4 evaluated PET-only RFs (E1), CT-only RFs (E2), PET/CT RFs (E3), and CBs (E4). Feature selection within these experiments identified important features and the best ML algorithms. Experiments 5 to 7 (E5-E7) investigated the predictive power by combining selected RFs from E1 to E3 with chosen CBs from E4. E8 E10 further combined selected RFs from E1 to E3 with all CBs.

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Statistics and model evaluation

Leave-one-out cross-validation was used to train and validate the ML models, addressing the small sample size. Model performance was assessed using the coefficient of determination (R^2), Pearson coefficient of correlation (ρ , Qvalue < .05) for kidneys, Spearman's rank correlation (ρ , Qvalue < .05) for lesions, mean absolute error, root meansquare-error (RMSE), and mean absolute percentage error in comparison to the ground truth. Mean absolute error, RMSE, and mean absolute percentage error were computed in Gy/GBq.

Results

In a cohort of 20 patients, 34 kidneys (LK and RK from each patient) were analyzed, with 3 patients missing full kidney data in the SPECT field. Additionally, 130 tumoral lesions >2 mL (mean = 43.03 ± 70.31 mL; range, 2.1-370.68 mL)

were included, predominantly 104 BMs, along with 19 LNMs and 7 STs. The data set comprised 124 quantitative Ga-PSMA PET RFs, 119 quantitative Ga-PSMA CT RFs, 3 morphologic features, 1 treatment history feature, 9 blood-test biomarkers, and 1 histopathological biomarker. Table 3 provides AD statistics in Gy and Gy/GBq for all 20 patients with mCRPC in this study. The kidneys have a mean AD of 0.88 \pm 0.34 Gy/GBq (5.98 \pm 2.31 Gy), ranging from 0.11 to 1.65 Gy/GBq (0.74-11.22 Gy). Tumoral lesions exhibit a mean AD of 2.36 \pm 2.10 Gy/GBq (16.05 \pm 14.28 Gy), ranging from 0.05 to 13.72 Gy/GBq (0.38-93.30 Gy).

The prediction performance of various ML algorithms was evaluated using RFs and CBs across E1 to E10 experiments. Tables 4 and 5 present the names of the selected variables for each experiment from E1 to E10, for kidneys and lesions, respectively. The correlation coefficients (ρ) between each selected feature and the mean ADs are reported in parentheses next to the variable names. Pearson's correlation coefficient is used for kidneys, and Spearman's rank correlation is used for lesions, with Benjamini-Hochberg correction applied (Qvalue < .05). Tables 6 and 7

Table 3 AD for kidneys and tumoral lesions of all 20 patients (in Gy and Gy/GBq)

Target (no.)	Range of AD (Gy)	Mean (±STD) of AD (Gy)	Range of AD per administered dose (Gy/GBq)	Mean (±STD) of AD per administration dose (Gy/GBq)
Tumoral lesions (n = 130)	0.38-93.30	16.05 ± 14.28	0.05 - 13.72	2.36 ± 2.10
Kidneys (n = 40)	0.74-11.22	5.98 ± 2.31	0.11-1.65	0.88 ± 0.34
<i>Abbreviation:</i> AD = absorbed do	ose.			

Table 4 The name of selected variables for kidneys in each experin
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Kidneys	
Experiment	No. and name of final selected variables (Pearson correlation coefficient with estimated AD, Qvalue < .05)
E1	5: IB_IntensitySkewness ($\rho = -0.44$), IH_IntensityHistogram10thPercentile ($\rho = 0.49$), GLRLM_GreyLevelNonUniformity ($\rho = -0.49$), NGTDM_Busyness ($\rho = -0.63$), and GLSZM_SmallZoneEmphasis ($\rho = 0.59$)
E2	4: MORPHOLOGICAL_SurfaceToVolumeRatio ($\rho = -0.47$), IH_IntensityHistogram25thPercentile ($\rho = -0.41$), GLCM_ClusterProminence ($\rho = -0.39$), GLSZM_NormalisedZoneSizeNonUniformity ($\rho = -0.40$)
E3*	8: RF1_PET: IH_IntensityHistogramMedian ($\rho = 0.62$), RF2_PET: IH_MaximumHistogramGradien ($\rho = -0.65$), RF3_PET: IB_IntensitySkewness ($\rho = -0.45$), RF4_PET: GLSZM_SmallZoneEmphasis ($\rho = -0.59$), and RF5_PET: NGTDM_Busyness ($\rho = -0.63$) RF6_CT: IH_IntensityHistogramInterquartileRange_CT ($\rho = 0.39$), RF7_CT: GLCM_ClusterProminence_CT ($\rho = -0.39$), and RF8_CT: GLSZM_NormalisedZoneSizeNonUniformity_CT ($\rho = -0.40$)
E4	4: RBC (ρ = -0.55), CR (ρ = 0.48), HCT (ρ = -0.49), and ALP (ρ = -0.48)
Abbreviations: AD * Row E3 correspond	e = absorbed dose; IB = intensity-based; IH = intensity-histogram. ds to symbols such as RF1_PET to RF8_CT, related to Figure 7.

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Tumoral lesic	ons
Experiment	No. and name of final selected variables (Pearson correlation coefficient with estimated AD, Qvalue < .05)
E1	7: IH_IntensityHistogramMode (ρ = 0.54), IH_IntensityHistogramCoefficientOfVariation (ρ = 0.47), GLCM_JointEntropyLog2 (ρ = 0.67), GLSZM_SmallZoneEmphasis (ρ = 0.54), GLSZM_ZoneSizeEntropy (ρ = 0.51), GLSZM_ZoneSizeNonUniformity (ρ = 0.76), and GLSZM_NormalisedZoneSizeNonUniformity (ρ = 0.54)
E2	7: MORPHOLOGICAL_SurfaceToVolumeRatio ($\rho = -0.22$), IH_IntensityHistogramMode ($\rho = -0.33$), IH_IntensityHistogram10thPercentile ($\rho = -0.28$), GLCM_DifferenceAverage ($-\rho = 0.43$), GLRLM_LongRunsEmphasis ($\rho = 0.50$), GLSZM_LargeZoneLowGreyLevelEmphasis ($\rho = 0.24$), GLSZM_ZonePercentage ($-\rho = 0.54$), and NGTDM_Complexity ($\rho = -0.32$)
E3*	10: RF1_PET: IH_IntensityHistogram10thPercentile ($\rho = 0.60$), RF2_PET: IH_IntensityHistogramMode ($\rho = 0.54$), RF3_PET: GLCM_JointEntropyLog2 ($\rho = 0.67$), RF4_PET: GLSZM_NormalisedGreyLevelNonUniformity ($\rho = -0.47$), RF5_PET: GLSZM_NormalisedZoneSizeNonUniformity ($\rho = 0.54$), RF6_PET: GLSZM_ZoneSizeNonUniformity ($\rho = 0.76$) RF7_CT: IB_IntensityKurtosis_CT ($\rho = 0.22$), RF8_CT: IB_StandardDeviation_CT ($\rho = -0.45$), RF9_CT: GLCM_NormalisedInverseDifferenceMoment_CT ($\rho = 0.24$), and RF710_CT: GLSZM_ZoneSizeVariance_CT ($\rho = 0.22$)
E4	2: PSA ($\rho = 0.41$) and ALP ($\rho = -0.24$)
Abbreviation * Row E3 corre	us: AD = absorbed dose; IB = intensity-based; IH = intensity-histogram. esponds to symbols such as RF1_PET to RF8_CT, related to Figure 7.

Table 5 The names of selected variables for lesions in each experiment

summarize the test set results for the kidneys and lesions, respectively.

Experiment E3 for kidneys, using a combination of PET and CT RFs with the AdaBoost model, achieved an R^2 of 0.58. This was significantly improved in E7,

where the integration of important CBs (red blood cell [RBC], CR, Hematocrit [HCT], and alkaline phosphatase [ALP]) with E3 variables led to an R^2 of 0.76 using the ETR model. The highest performance was noted in E10, incorporating all CBs and RFs from E3,

Table 6Experiment-wise selection of variables and optimal ML algorithms, with evaluation metrics on the test set for pre-dicting kidney mean ADs

Experiment (No. of selected variables)*	Best regression ML model	R ²	ho (Pearson coefficient, Qvalue < .05)	MAE (Gy/ GBq)	RMSE (Gy/ GBq)	MAPE (%)
E1 (5)	AdaBoost	0.53	.78	0.17	0.21	0.31
E2 (4)	KNR	0.41	.61	0.18	0.23	0.35
E3* (8)	AdaBoost	0.58	.74	0.17	0.20	0.25
E4 (4)	AdaBoost	0.64	.82	0.15	0.18	0.19
E5: E1 + E4 (9)	GBR	0.75	.86	0.12	0.16	0.25
E6: E2 + E4 (8)	ETR	0.70	.83	0.13	0.18	0.27
E7: E3 + E4 (12)	ETR	0.76	.87	0.12	0.15	0.23
E8: E1 + whole CBs (19)	GBR	0.85	.91	0.09	0.12	0.18
E9: E2 + whole CBs (18)	ETR	0.83	.88	0.09	0.13	0.19
E10: E3 + whole CBs (22)	ETR	0.87	.93	0.09	0.11	0.16

Abbreviations: AD = absorbed dose; CB = clinical biomarker; ETR = extra trees regressor; GBR = gradient-boosting regressor; KNR = K neighbors regressor; MAE = mean absolute error; MAPE = mean absolute percentage error; ML = machine learning; RMSE = root mean-square-error. * The names of the selected variables for each experiment are listed in Table 4.

Experiment (No. of selected variables)*	Best regression ML model	R ²	ho (Spearman's rank, Qvalue < .05)	MAE (Gy/GBq)	RMSE (Gy/GBq)	MAPE (%)
E1 (7)	KNR	0.67	.82	0.83	1.26	0.53
E2 (7)	GBR	0.58	.76	0.96	1.46	0.85
E3* (10)	RFR	0.69	.83	0.78	1.21	0.49
E4 (2)	RFR	0.53	.74	0.99	1.53	0.75
E5: E1 + E4 (10)	RFR	0.7	.83	0.76	1.19	0.51
E6: E2 + E4 (9)	ETR	0.66	.81	0.82	1.29	0.53
E7: E3 + E4 (13)	GBR	0.75	.87	0.71	1.08	0.45
E8: E1 + Whole CBs (21)	ETR	0.74	.85	0.74	1.12	0.47
E9: E2 + Whole CBs (21)	ETR	0.76	.87	0.71	1.07	0.44
E10: E3 + Whole CBs (24)	GBR	0.77	.87	0.68	1.04	0.43

 Table 7
 Experiment-wise selection of variables and optimal ML algorithms, with evaluation metrics on the validation set for predicting the mean ADs in tumoral lesions

Abbreviations: ETR = extra trees regressor; GBR = gradient-boosting regressor; KNR = K neighbors regressor; MAE = mean absolute error; MAPE = mean absolute percentage error; ML = machine learning; RFR = random forest regressor; RMSE = root mean-square-error.

The names of the selected variables for each experiment are listed in Table 5.

where the ETR model achieved an R^2 of 0.87 and reduced errors.

For tumoral lesions, similar trends were observed with enhanced predictive accuracy in the latter experiments. Experiment E3, which combined PET and CT RFs, resulted in an R^2 of 0.69 using the random forest regressor model. This performance was further improved in E7, where the GBR model, integrating prominent CBs (prostate-specific antigen [PSA] and ALP), achieved an R^2 of 0.75. The optimal results were seen in E10, where the GBR model, incorporating all CBs and variables from E3, provided the highest accuracy with an R^2 of 0.77 and minimized errors. These results underscore the efficacy of incorporating comprehensive feature sets for improved prediction of ADs in both kidneys and tumoral lesions.

Figure 4 compares the predicted ADs with the estimated ADs in the optimal scenarios derived from Tables 6 and 7, specifically E7 and E10, for both the kidneys and the lesion.



Fig. 4. Comparison of pretherapy predicted mean absorbed doses (ADs) with measured ADs using the best models: (a) E7 and (b) E10 for kidneys, and (c) E7 and (d) E10 for lesions, as derived from the results presented in Tables 6 and 7.

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Panels a and b show kidney analysis at E7 and E10 (Table 6), whereas panels c and d show lesion analysis at E7 and E10 (Table 7), respectively. The identity line indicates alignment between predicted and measured ADs, with closer clustering around it suggesting better R^2 in AD prediction.

The mean \pm SD of the absolute dose differences between the predicted and measured ADs in the kidneys was 0.13 \pm 0.10 Gy/GBq for E7 and 0.09 \pm 0.08 Gy/GBq for E10. For the lesions, the mean \pm SD differences were 0.72 \pm 0.85 Gy/GBq for E7 and 0.68 \pm 0.85 Gy/GBq for E10. Figure 5 displays SHapley Additive exPlanations (SHAP) summary plots for the top 20 features in the E10s, illustrating their importance and effects on predicting ADs in kidneys (panel a) and lesions (panel b), respectively. These plots provide a post-hoc explanation of the AI models, offering insight into feature importance and their impact on model predictions. Each point represents a SHAP value, with features sorted by importance on the y-axis, SHAP value magnitude on the x-axis, and feature value indicated by color. IntensityHistogramMedian and GLSZM_ZoneSizeNonUniformity RFs from Ga-PSMA PET were the most significant contributors to predicting mean AD in kidneys and lesions, respectively. Moreover, Figure 6a,b illustrates Bland-Altman (B-A) plots for model predictions, provided by E3 and E10 for kidneys, whereas Figure 6c,d depicts the corresponding plots for the lesions. A B-A analysis would be a suitable method to quantify and explain the dose differences between the 2 methods (measured vs predicted), providing visual and statistical insights into their agreement.

The horizontal axis in the B-A plot represents the mean of measured and the model-predicted ADs, whereas the vertical axis shows the relative percent difference (RPD) between ML model predictions and measured AD, defined as RPD = $(AD_{pred} - AD_{meas}/AD_{meas}) \times 100$ %. The mean is represented by a blue dashed horizontal line, whereas the

95% confidence interval (CI; mean \pm 1.96 × SD) is indicated by red dashed lines. According to Figure 6a, for kidneys, the mean RPD with a 95% CI is 4.63% (-57.83% to 67.10%) for model E7 and 3.74% (-38.97% to 46.45%) for model E10. Similarly, Figure 6b shows for lesions, the mean RPD is 10.06% (-75.51% to 95.64%) for E7 and 8.72% (-75.42% to 92.86%) for E10.

Figure 7 shows the correlation analysis via chord diagrams. Figure 7a illustrates correlations between 8 selected RFs and 4 selected CBs for kidneys in E7, whereas Figure 7b depicts correlations for kidneys in E10 between 8 selected RFs and all CBs. Similarly, panels c and d depict these correlations for lesions in E7 and E10, respectively. Each segment represents an RF or CB, with chord thickness indicating the relationship strength. For instance, RF1_PET in panel a corresponds to INTENSITYHISTOGRAM_IntensityHistogramMedian from Table 4, E3. The correlations suggest that while certain texture RFs are highly dimensional and cannot be observed by the naked eye, specific combinations of these RFs can be attributed to specific characteristics represented by CBs.

Discussion

Pretreatment AD predictions are valuable for optimizing patient selection and tailoring RPTs through individualized dosimetry. Predicting the ADs to tumor and OAR before RLT can enhance treatment efficacy by facilitating the development of personalized treatment plans within the diagnostic framework of theranostics.⁴³ A major challenge in predicting posttherapy dose distribution from pretherapy imaging arises from a substantial information gap. Pretherapy imaging captures tracer uptake at a single time point, typically 1 hour after injection, whereas posttherapy dose



Fig. 5. SHapley Additive exPlanations (SHAP) summary plots of the top 20 features in E10 for (a) kidneys and (b) lesions, ranked by importance, showing their impact on the predictive external tree regressor (ETR) and gradient-boosting regressor (GBR) models, respectively.



Fig. 6. Bland-Altman (B-A) plots showing the relative percentage difference between dose prediction (by model) and measurement versus the mean of measured and predicted dose in kidneys (a) selected PET/CT RFs and CBs (E7), (b) selected PET/CT RFs and all CBs (E10), and in lesions (c) selected PET/CT RFs and CBs (E7), (d) selected PET/CT RFs and all CBs (E10). *Abbreviations:* CB= clinical biomarker; CT = computed tomography; RF = radiomic feature; SPECT = single photon emission computed tomography.

distribution represents the cumulative effect of radiationmatter interactions over a prolonged and dynamic period. Moreover, the therapeutic tracer Lu-PSMA is administered at much higher activity levels compared to the imaging tracer Ga-PSMA, and their PSMA ligands, although similar, are not identical. Additionally, biodistribution can be affected by factors such as tumor burden, injected activity, and the quantity of coadministered cold ligands.^{43,44}

The theranostic approach relies on the similar pharmacokinetics of the imaging and therapeutic tracers (PSMA-11 and PSMA-617), allowing for a qualitative prediction of the posttherapy dose before treatment.⁴⁴ Previous research has demonstrated a correlation between SUV values from pretherapy imaging and posttherapy dose distribution.^{20,45} These findings suggest that incorporating pretreatment data can aid in estimating individualized posttherapy dosimetry, thereby minimizing the risk of under- or overestimating variations in biodistribution.^{19,46} To the best of our knowledge, this study is the first to explore regression ML models for predicting kidney and tumoral lesion ADs in Lu-PSMA RLT using Ga-PSMA PET/CT RFs and nonimaging CBs, with MC-based AD results as reference points for model construction.

Table 3 presents the mean, SD, and range of ADs in Gy and Gy/GBq for kidneys and lesions. The kidney AD in this study was 0.88 \pm 0.34 Gy/GBq, consistent with previously reported ranges, such as 0.88 \pm 0.4 Gy/GBq, 0.75 \pm 0.19 Gy/GBq, 0.99 \pm 0.31 Gy/GBq, 0.67 \pm 0.27 Gy/GBq, and 0.67 \pm 0.24 Gy/GBq. Similarly, the mean lesion AD was 2.36 \pm 2.10 Gy/GBq, comparable with other reported values, including 3.25 \pm 3.19 Gy/GBq, 1.7 \pm 1.13 Gy/GBq, and 3.47 \pm 2 Gy/GBq, as summarized in a systematic review and meta-analysis providing a comprehensive comparison.¹²

The kidneys have traditionally been considered dose-limiting organs for RPTs, with cumulative AD limits of 23 Gy or 27 Gy derived from external beam radiation therapy.^{13,28,47} However, there is an ongoing debate within the field regarding the relevance of these thresholds for RPT.^{48,49} In this study, the absence of dosimetry data for the kidneys during each therapy cycle necessitated estimating the dose for the remaining cycles by presuming a 5% increase in AD per cycle. This approximation relies on published data indicating a 20% increase in AD between cycles 1 and 4.^{50,51} Using this approximation, the cumulative dose for some patients remained below the established 23 Gy or 27 Gy thresholds, allowing flexibility to exceed the standard 7.4 GBq dose. There is, however, growing advocacy for revisiting these limits based on clinical experience with systemic radiopharmaceuticals.⁵²

In the treatment planning methodology outlined in this study, 10 ML regression algorithms were evaluated. The best experiment (E10) scored an RMSE of 0.11 for kidneys and 1.04 for lesions, employing ETR and GBR, respectively. This evaluation compared pretherapy-selected RFs from Ga-PSMA PET/CT scans with all CBs to posttherapy Lu-PSMA RLT ADs. The findings indicate that integrating RFs with CBs enhances the predictive accuracy of ML models compared with using them alone. Nonlinear-based ML models, particularly tree-based ML algorithms outperformed linear-based ones in generating accurate predictions through capturing complex relationships in data.

To understand the clinical relevance of RFs for predicting ADs in kidneys and lesions, the significant predictive RFs from this study mostly belonged to second-order or texture classes, indicating tissue heterogeneity in the targets.¹⁷ E1 and E2 in Tables 6 and 7 reveal that PET RFs played a more substantial role than CT RFs in AD prediction models. However, the specific information provided by CT RFs cannot be overlooked. Combining PET and CT RFs as indicated in E3, improves prediction accuracy for both kidneys and lesions, highlighting the complementary nature of these modalities.

This study hypothesized that incorporating biomarkers into ML models could account for patient-specific kinetics affecting ADs, which are difficult to derive from imaging a short-lived surrogate. This integration is expected to enhance predictive power beyond that provided by Ga-PSMA PET/CT RFs alone. In this regard, when RFs from PET, CT, and PET/CT (E1-E3) were combined with selected CBs (E4), the results exhibited improved values across all evaluation metrics. This underscores the significant role of CBs and their informative nature, enriching imaging data with valuable clinical information. This enhancement is evident in E5 to E7 of Tables 6 and 7 for kidneys and lesions, respectively. Furthermore, combining selected PET, CT, and PET/CT RFs from E1-E3 with all collected CBs (14 CBs) during E8 to E10 demonstrated notable efficiency improvements, particularly with PET/CT RFs (E3). The best outcomes for kidneys and tumors were achieved in E10.

Incorporating all CBs (E8-E10) enhanced the results by allowing the models to capture a broader range of patientspecific biological and physiological variations that influence ADs. Although "optimal" CBs are selected based on their predictive strength, including all CBs integrate potentially synergistic effects and account for multivariate correlations. This comprehensive approach enriches the feature set, reducing bias and increasing the predictive power of the models by leveraging complementary information that may not be apparent in isolated CBs. This is particularly relevant given the heterogeneity in patients with mCRPC, where multiple factors collectively influence the pharmacokinetics and biodistribution of radioligands.

Figure 5 displays SHAP summary plots for E10 in kidneys (a) and lesions (b), respectively, assigning contribution scores to selected features. These plots unveil how each feature contributes to the model's prediction, enhancing comprehension of black-box ML models. In Figure 5a, the first feature, INTENSITY-HISTOGRAM_IntensityHistogram-Median, ($\rho = 0.62$ with AD), a PET RF, represents the median intensity value derived from a kidney's intensity histogram. The second contributor feature, NGTDM_Busyness ($\rho = -0.63$ with AD), a PET RF, quantifies voxel intensity changes within the neighborhood, suggesting a more homogenous tissue structure with lower busyness values.

The 2 most contributing RFs for lesions in E10 shown in Figure 5b are GLSZM_ZoneSizeNonUniformity ($\rho = 0.76$ with AD) and GLCM_JointEntropyLog2 ($\rho = 0.67$ with AD) PET RFs. ZoneSizeNonUniformity RF quantifies the variability in the size of neighboring voxel regions with similar intensity. A high ZoneSizeNonUniformity value indicates a wider variation in zone sizes, suggesting greater heterogeneity. Entropy represents the level of uncertainty or disorder within a system. In GLCM, joint entropy assesses the randomness or complexity of the voxel intensity combinations in the co-occurrence matrix. A higher joint entropy value signifies a greater degree of randomness or complexity in the spatial relationships of intensities, indicating a more heterogeneous texture.

According to E4 in Table 4, for the kidney analysis, the most significant CBs are RBC ($\rho = -0.55$), CR ($\rho = 0.48$), HCT ($\rho = -0.49$), and ALP ($\rho = -0.48$). For lesions (E4, Table 5), PSA ($\rho = 0.41$), and ALP ($\rho = -0.24$) stand out as the most crucial CBs. Furthermore, examining the SHAP summary plots in Figure 5a for kidneys reveals that HCT and ALP are the top contributors among CBs in the E10 using the ETR model. They rank 4th and 5th, respectively, following 3 PET RFs. Similarly, in lesions, based on Figure 5b, PSA and ALP rank 5th and 6th among variables after 4 PET RFs but emerge as the top 2 contributors among all CBs in the E10 model using GBR.

Three CBs—RBC, HCT, and ALP—show a reverse correlation. The etiology of anemia in advanced PCa is multifactorial, involving castration, poor nutrition, bone marrow infiltration, drug toxicity, and chronic inflammation. Androgen deprivation-mediated anemia is because of some different factors; testosterone affects erythropoietin formation in the kidney and bone marrow erythropoiesis. Additionally, some peripheral changes are detected, such as a 10% and 40% decrease in RBC mass and RBC diameter, respectively, and an increase in osmotic fragility.⁵³ A decrease in RBC as well as HCT is related to anemia-

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inducing and worsening hypoxia as well as contributing to renal dysfunction progression. Treatment of anemia may decline the nephron destruction rate. Hypoxia could be an initiative or enhancing factor for kidney disease, causing inflammation and increased migration of leukocytes, encoding the 2-integrin adhesion molecules.⁵⁴

The reverse correlation of ALP with kidney AD could be because of extreme radioligand pooling in extensive lesions and thus lower proportion reaches both kidneys.⁵⁵ Creatinine (CR) is a well-established indicator of kidney function and exhibits a significant direct correlation with kidney ADs. This correlation aligns with biological expectations and findings from other studies, where higher Cr levels corresponded to increased ADs in the kidneys.²²

PSA shows a significant direct correlation, and ALP shows a significant reversed correlation with ADs in lesions among all CBs. Higher PSA and lower ALP levels indicate more PSMA expression in lesions (differentiated PCa) and more expectation for response to RLT. The direct relationship between PSA level and PCa recurrence is well-documented.^{56,57} Differentiation between aggressive and indolent PCa remains challenging, affecting under/over-treatment.

PSMA upregulation correlated with PCa, especially in advanced cases, and is an independent association with PSA recurrence in high-risk patients.58 Regarding most metastatic lesions in the bone as well as no liver metastasis and normal liver function tests in our patients, increased ALP originated from bone. ALP is reflective of osteoblast-like cell phenotype within the microenvironment of bone,⁵⁹ showing bone turnover and osteoblastic activity.⁶⁰ As found in previous studies, an increase because of ALP demonstrates a negative effect on the patient's prognosis.^{61,62} Moreover, ALP levels are variably affected by each type of treatment and also there are more details in each drug subset. Also, based on response to a particular treatment, it may decrease or increase during treatment. ALP as a rational prognostic marker should be routinely monitored, alongside other markers of disease progression such as PSA, PSA doubling time, and PSMA expression imaging in patients with PCa, especially mCRPC.

According to B-A plots in Figure 6, an important observation is the trend of decreasing mean RPD and narrowing CIs from model E7 to model E10 for both kidneys and lesions. This indicates that increasing the extent of data and adding CBs to the model improves accuracy and reliability. About 94% (32/34) of kidney data points and 97% (126/130) of lesion data points fall within the confidence CIs, indicating strong agreement.

The B-A plots reveal systematic trends in the model predictions, providing insight into the limitations of our hybrid scintigraphy/SPECT/CT-based dosimetry approach. For kidney ADs, both models show a slight overestimation of the therapy-delivered AD, with mean RPD values of 4.63% for E7 and 3.74% for E10. Notably, the narrower CI of E10 suggests reduced prediction variability compared to E7, highlighting its improved prediction stability. However, these results should be interpreted with caution, as kidney dosimetry remains influenced by several sources of uncertainty, including segmentation accuracy, reconstruction, and assumptions underlying the AD calculation. Peterson et al²² conducted a similar analysis to compare pretherapy AD predictions from univariable models based on PET uptake and eGFR with the therapy-delivered AD. Their findings reported a mean relative percent error of 4.8% (95% CI, -38.3% to 48.0%) for the PET uptake-based model and 9.1% (95% CI, -56.2% to 74.5%) for the eGFR-based model.

In contrast, the prediction of lesion ADs shows substantially higher variability. The B-A plots for both E7 and E10 display a wide scatter of points across the full range of mean ADs, with broad limits of agreement (eg, -75.51% to 95.64% for E7 and -75.42% to 92.86% for E10). Unlike the kidney plots, where data points are relatively concentrated around the mean difference line, the lesion plots lack a clear central tendency and exhibit substantial dispersion. The higher variability might be because of factors such as lesion heterogeneity, smaller lesion size, and PVE. These findings suggest that observed correlations for lesions should be interpreted cautiously since prediction errors may fall within or exceed typical dosimetric uncertainties. Lesion heterogeneity and imaging limitations are key challenges, indicating the need for further improvements in prediction methodologies.

The chord diagrams in Figure 7 effectively illustrate the complex correlation structure between selected RFs and CBs for both kidneys and lesions in E7 and E10. The density and distribution of chords provide insights into how incorporating all CBs in E10 influenced the model. For kidneys, E7 (panel a) demonstrates more focused correlations, with RFs like RF1_PET (INTENSITY-HISTOGRAM_IntensityHistogramMedian; Table 4) strongly associated with specific CBs such as CR and RBC. In contrast, E10 exhibits a denser and more interconnected network, involving a wider range of CBs such as HB and WEIGHT, reflecting the broader physiological or systemic influences captured under E10. A similar trend is observed for lesions: E7 (panel c) highlights distinct RF-CB relationships, such as the correlation between RF6 PET (GLSZM_ZoneSizeNonUniformity; Table 5) and PSA. Meanwhile, E10 exhibits increased complexity by incorporating additional CBs such as hemoglobin (HB) and calcium (CA). The transition from narrower to denser chord structures from E7 to E10 underscores the enhanced complexity and predictive capacity achieved by including all CBs. This broader network allows the model to capture richer systemic and multifactorial relationships between RFs and CBs, ultimately improving dose prediction accuracy for both kidneys and lesions.

The study encountered several limitations. First, the small sample size and lacked validation on an independent patient cohort, potentially constrain the generalizability of the models. Moreover, all PET/CT and SPECT/CT imaging were conducted using specific scanner models with standardized reconstruction protocols. Although this ensured

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Fig. 7. Chord diagram of the correlation between radiomics features (RFs) and clinical biomarkers (CBS). (a) E7 in kidneys, (b) E10 in kidneys, both via Pearson coefficient of correlation, (c) E7 in lesions, and (d) E10 in lesions, both via Spearman's rank correlation. Links represent significant correlations (*Q*value < .05), with width indicating strength.

consistency, the findings may not be directly applicable to other scanner types or reconstruction settings, which could influence feature extraction and AD calculations. Future studies should include imaging data from diverse scanners to improve model robustness. Second, our investigation focused on PET/CT and biomarkers available before the initial RLT cycle. Third, our assessment of predicted ADs was limited to kidneys and lesions after the first RLT cycle, overlooking other OARs such as salivary glands, typically requiring 3-bed positions in SPECT/CT imaging to cover OAR in RLT comprehensively.

Fourth, manual segmentation of kidneys and lesions, though carefully reviewed, may introduce interobserver variability, especially for lesions with diffuse boundaries. Moreover, coregistration of imaging modalities, while performed rigorously, might contribute to minor alignment errors affecting TIA and dose calculations. Furthermore, the segmentation process, particularly for lesions, was exceedingly time-consuming, demanding precise delineation on both SPECT/CT and PET/CT scans. To overcome this obstacle, integrating deep learning (DL) methods for automated or semiautomated segmentation and registration emerges as a promising solution.⁶³⁻⁶⁵ These advanced techniques have the potential to streamline the segmentation process, reducing the time and effort required by experts.

Furthermore, pretherapy Ga-PSMA PET/CT scans were performed within 2 months of pretreatment, with varying timing for each patient, as some scans were conducted a few

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days before therapy and others up to 2 months prior. This variability could introduce temporal fluctuations in tumor or organ conditions. Standardizing imaging timelines closer to therapy could enhance prediction accuracy. Moreover, the timing of SPECT was \sim 48 h and scintigraphy was conducted approximately 4, 48, and 72 hours postinjection, which was not consistent for all patients. This variability was because of the availability of the imaging system at these intervals. However, aligning the timing of scintigraphy more precisely across all patients could further reduce temporal discrepancies and improve the accuracy of treatment predictions.

Among the various dosimetry techniques, MC simulation is recognized as a highly precise method for personalized dosimetry, particularly suitable for scenarios involving heterogeneous activity distributions and media.^{13,29} In this study, MC simulation was employed to calculate ADRMs, enhancing the accuracy of the ground-truth AD data used for model development. However, MC simulation is computationally intensive, time-consuming, and requires complex setup processes. Future work should focus on developing and implementing fast, efficient MC-based tools to facilitate the generation of ground-truth MC-based data, which are essential for training and validating models for pretreatment dosimetry.

Another limitation of this study is using a hybrid scintigraphy/SPECT imaging approach for TIA coefficients calculation, as multiple-time point pure SPECT/CT imaging was not feasible because of its lengthy acquisition time, higher cost, and associated patient discomfort. Previous research has demonstrated that SPECT/CT imaging protocols yield more consistent and less variable results compared to planar imaging methods.⁶⁶ Although combining planar imaging with 3D SPECT improves accuracy over planar imaging alone, it still yields region-specific TIA coefficients instead of more accurate voxel-specific values from multiple-time point SPECT.^{10,29} Planar imaging has limitations, including lower spatial resolution, lack of 3D tissue distribution, and limited anatomical context, which can affect dosimetry precision.

To address these limitations, single-time point posttreatment SPECT/CT imaging is proposed.^{67,68} Although less accurate than multiple-time point imaging, using 2 or more scans during the first treatment cycle to determine patient-specific biokinetics, followed by the singletime point framework for subsequent cycles, could improve dosimetry accuracy and feasibility.⁶⁹ Moreover, recent advancements in simplified dosimetry methods, including reduced SPECT imaging acquisition times, are paving the way for personalized treatment planning to improve the efficacy of RLT.^{35,70}

Another bottleneck of this study is the reliance on target organ contours from pretherapy PET imaging and the RFs derived from them, without accounting for intraorgan dose distribution. Variations in pharmacokinetics within an organ may complicate the accuracy of pretherapy dosimetry predictions. Although the study supports predicting ADs at the organ level, extending this to the voxel level requires further research. Addressing spatial heterogeneity in radiopharmaceutical distribution and energy deposition will require DL approaches or integrating the physiologically based pharmacokinetic model into DL, to analyze intraorgan heterogeneity and explore pretherapy dosimetry prediction.^{43,44}

Finally, although we demonstrated the feasibility of integrating pretherapy Ga-PSMA PET RFs with CBs, this approach could be expanded to include additional biomarkers and more histopathological features with larger sample sizes to ensure robust statistical efficacy.

An important consideration in dosimetry is that each step in the workflow can introduce uncertainty in AD estimates. Factors such as imaging protocol, organ and lesion segmentation, decay estimation, and the choice of dosimetry method and software all contribute to variability.⁶⁶ Although the method or software has a minimal impact, segmentation, curve fitting, and integration are more significant sources of variation.⁷¹ Therefore, standardizing these processes is essential to minimizing variability.

Conclusions

The study examined the efficacy of incorporating Ga-PSMA PET-derived RFs alongside CBs to predict ADs in tumors and kidneys for patients with mCRPC undergoing Lu-PSMA RLT. This investigation into noninvasive dose prediction could facilitate the development of individualized treatment planning for RLT. However, further validation with an expanded patient cohort, particularly from external data sets, is crucial to substantiate the performance of the ML models and to provide a robust decision-support tool before clinical adoption.

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