Kinetic modeling of $^{68}$Ga-PSMA-11 and validation of simplified methods for quantification in primary prostate cancer patients

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Abstract

Background: The positron emission tomography (PET) ligand $^{68}$Ga-Glu-urea-Lys(Ahx)-HBED-CC ($^{68}$Ga-PSMA-11) targets the prostate-specific membrane antigen (PSMA), upregulated in prostate cancer cells. Although $^{68}$Ga-PSMA-11 PET is widely used in research and clinical practice, full kinetic modeling has not yet been reported nor have simplified methods for quantification been validated. The aims of our study were to quantify $^{68}$Ga-PSMA-11 uptake in primary prostate cancer patients using compartmental modeling with arterial blood sampling and to validate the use of standardized uptake values (SUV) and image-derived blood for quantification.

Results: Fifteen patients with histologically proven primary prostate cancer underwent a 60-min dynamic $^{68}$Ga-PSMA-11 PET scan of the pelvis with axial T1 Dixon, T2, and diffusion-weighted magnetic resonance (MR) images acquired simultaneously. Time-activity curves were derived from volumes of interest in lesions, normal prostate, and muscle, and mean SUV calculated. In total, 18 positive lesions were identified on both PET and MR. Arterial blood activity was measured by automatic arterial blood sampling and manual blood samples were collected for plasma-to-blood ratio correction and for metabolite analysis. The analysis showed that $^{68}$Ga-PSMA-11 was stable in vivo. Based on the Akaike information criterion, $^{68}$Ga-PSMA-11 kinetics were best described by an irreversible two-tissue compartment model. The rate constants $K_1$ and $k_3$ and the net influx rate constants $K_i$ were all significantly higher in lesions compared to normal tissue ($p < 0.05$). $K_i$ derived using image-derived blood from an MR-guided method showed excellent agreement with $K_i$ derived using arterial blood sampling (intraclass correlation coefficient = 0.99). SUV correlated significantly with $K_i$ with the strongest correlation of scan time-window 30–45 min (rho 0.95, $p < 0.001$). Both $K_i$ and SUV correlated significantly with serum prostate specific antigen (PSA) level and PSA density.

Conclusions: $^{68}$Ga-PSMA-11 kinetics can be described by an irreversible two-tissue compartment model. An MR-guided method for image-derived blood provides a non-invasive alternative to blood sampling for kinetic modeling studies. SUV showed strong correlation with $K_i$ and can be used in routine clinical settings to quantify $^{68}$Ga-PSMA-11 uptake.

Keywords: Prostate cancer, PSMA, PET/MR, Kinetic modeling, Arterial blood sampling, Image-derived input function, SUV
Background

The positron emission tomography (PET) ligand $^{68}$Ga-Glu-urea-Lys(Ahx)-HBED-CC ($^{68}$Ga-PSMA-11) has dramatically improved diagnostic imaging of prostate cancer. PSMA-11 targets the prostate-specific membrane antigen (PSMA), which is overexpressed in most prostate cancer cells [1]. Several studies have shown that the combination of $^{68}$Ga-PSMA-11 PET with anatomical information from magnetic resonance (MR) imaging provides superior detection and diagnostic accuracy of prostate cancers in comparison to other imaging techniques [2–6].

In routine clinical settings, the most commonly used method for PET quantification is the standardized uptake value (SUV). Its calculation is simple and routinely available in commercial imaging software packages. SUV is a semi-quantitative measure of the total activity concentration in a region-of-interest at a time point of the PET scan, normalized by the injected activity and the subject's weight. Studies have shown that SUV may differ between sites, when not controlling for image acquisition parameters such as scan time post-tracer injection, reconstruction algorithms, and attenuation and scatter corrections [7]. For accurate quantification of PET tracer uptake, pharmacokinetic compartmental modeling with dynamic scanning and arterial blood sampling is usually necessary. However, due to the long and complex acquisition protocols, simplified acquisition and analysis methods are adopted in clinical practice. Their correlation to compartmental modeling should however first be assessed [7].

Methods to extract image-derived blood information provide an attractive alternative to arterial blood sampling, as they noninvasively obtain the arterial blood curve during the PET scan. For whole-body PET, most methods outline regions-of-interest (ROIs) over the common iliac artery of the PET image to obtain the blood data. These methods, however, usually suffer from partial volume effects due to limited spatial resolution of the PET image. With combined PET/MR, the high-resolution MR image can be used to outline the arteries and when combined with partial volume correction approaches [8], provide a more accurate blood input function for kinetic modeling [9].

Previously published studies on the biodistribution and kinetics of $^{68}$Ga-PSMA-11 in prostate cancer patients reported increasing SUV in tumor lesions from early to late imaging and rapid blood clearance of $^{68}$Ga-PSMA-11 [10–12]. SUV correlated strongly with the net influx rate $K_i$, moderately with serum prostate-specific antigen (PSA) and weakly with Gleason score from biopsy [11, 12]. The authors used PET image-derived blood as input to the compartment model analysis, and omitted correction for plasma-to-blood ratio and study of labeled metabolites in plasma. To date, full kinetic modeling with arterial blood sampling and metabolite analysis has not yet been reported, nor has the use of simplified methods as SUV and image-derived blood data been validated.

Therefore, the objectives of the present study were to evaluate the kinetics of $^{68}$Ga-PSMA-11 using dynamic PET/MR scanning and arterial blood sampling, to validate the use of simplified methods for quantification and to correlate the results to patient, MR, and histopathological data.

Methods

Patients

Fifteen patients were included in this observational prospective study. The study was approved by the institutional ethics committee and informed consent was obtained from all individual participants included in the study. Inclusion criteria were histologically proven prostate cancer (Gleason score ≥ 6), with a tumour size of at least 0.6 cm in diameter on MR imaging. Only patients considered able to remain supine for at least one hour were included. Exclusion criteria were multiple malignancies, anticoagulant therapy and contraindications to MR imaging, such as claustrophobia and MR-incompatible implants. Serum PSA level had been measured previously and the prostate weight had been estimated by a previous MR scan. PSA density was calculated as serum PSA divided by the prostate weight.

PET/MR protocol

The patients underwent a 60-min dynamic PET scan in list-mode with the field of view over the pelvic area with arms down on a Biograph mMR scanner (Siemens, Germany), followed by a whole-body PET/MR scan for clinical purposes. At the start of the PET scan, a bolus injection of $^{68}$Ga-PSMA-11 (median 191.6 MBq, range 103.9–231.3 MBq) was administered intravenously and flushed with 40 mL of saline. $^{68}$Ga-PSMA-11 was synthesized according to Eder et al. [13].

We used a 24-channel spine radiofrequency coil integrated within the MR bed and three surface body coils (6 channels each) to cover the thorax, abdomen, and pelvis. The following MR data were acquired during the PET scan: axial T1 volumetric interpolated breath-hold examination (VIBE) Dixon (18 s), axial T2 half-Fourier single shot turbo spin echo (HASTE) without fat suppression with breath-holding (23 s) and axial diffusion-weighted imaging without breath-holding (2 min 19 s). PET data were reconstructed with a 3D ordered-subsets expectation maximization (OSEM) algorithm (3 iteration, 21 subsets, matrix $256 \times 256$, 4 mm Gaussian filter) and corrected for decay, scatter, and attenuation using Dixon-based MR sequences. The list mode data were reconstructed into 28 frames ($10 \times 30$ s, $5 \times 60$ s, $5 \times 120$ s, and $8 \times 300$ s).
Image analysis
The reconstructed PET/MR images were analyzed by a board-certified nuclear medicine physician and a radiologist using the software syngo.via (Siemens, Germany). The analysis included visual assessment of the number and types of lesions. Lesion TACs in unit Bq/mL were derived from volumes-of-interest (VOIs) using isocount threshold of 40% of maximum SUV on late PET images (last 15 min of scan) with the location confirmed on the T2-weighted MR images. Spherical VOIs of 1 mL were outlined on normal prostate and gluteus muscle to derive normal tissue TACs. MR images were analyzed using the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) [14] and the apparent diffusion coefficients (ADC) and lesion sizes were measured.

SUV in unit g/mL was calculated using the following formula: SUV = tissue concentration (kBq/mL)/(injected dose (MBq)/subject’s body weight (kg)). Mean SUV, which is the average SUV within a volume, was calculated for all VOIs.

Arterial input function
Arterial blood activity was measured by continuous blood sampling from the radial artery during the first 10 min using an automatic blood sampling device with 1 s temporal resolution (Twilite, Swisstrace GmbH, Switzerland). The blood sampling device was connected to a shielded pump (B Braun Infusomat Space), using flow rates 4.17 mL/min for the first 7 min, then 2.5 mL/min for the remaining 3 min. The blood sampling device had been calibrated previously to the PET/MR scanner. Manual arterial blood samples (4.9 mL) were collected in heparinized tubes at 6 time points (approximately 3, 7, 15, 25, 40, and 60 min post-injection), while the automatic blood sampling was briefly paused.

The manual blood samples were immediately put on ice and centrifuged to separate plasma. Whole blood and plasma-activities were measured in a gamma counter (Triathler, HIDE, Finland), which had been calibrated previously to the PET/MR scanner.

The arterial input function (AIF) was generated from the blood sampler curve corrected for decay, background, and dispersion, and resampled using the PSAMPLE software (PMOD, Switzerland). Using an in-house MATLAB program, the AIF was merged with the decay-corrected manual whole blood samples to get a 60-min AIF. This whole blood AIF was then converted into a plasma AIF using the average plasma-to-blood activity ratios from the manual samples for each subject.

Metabolite analysis
The plasma samples were analyzed for possible labeled metabolites using an ultra-high-pressure liquid chromatography (UHPLC) method. The samples were filtered by centrifugation at 20,000×g for 10 min at 4 °C using a filter with a molecular weight cut-off of 3 kDa and analyzed on a 1290 Infinity II UHPLC system (Agilent Technologies, USA) equipped with a radioactivity detector (Eckert & Ziegler, Germany). A volume of 100 μL was loaded using automatic injection and the samples were maintained at 4 °C. The analytical column was a Phenomenex Kinetex® reverse-phase C18 column (100 mm × 3 mm; 2.6 μm), maintained at 25 °C with water + 0.1% trifluoroacetic acid (TFA) (mobile phase A; 95%) and acetonitrile + 0.1% TFA (mobile phase B; 5%) at flow rate 0.8 mL/min. Gradient of mobile phase B was 5–10% (0.0–0.5 min); 10–30% (0.5–7.0 min); 30–5% (7.0–7.5 min); 5% (7.5–15.0 min). Due to the low activity concentration, UHPLC fractions were collected every 20 s and counted in an automatic gamma counter (Wizard 2TM 3” 2480, Perkin Elmer, USA). Measured activity was plotted as a function of time and compared to the retention time of a standard solution containing 68Ga-PSMA-11, analyzed using the same chromatographic protocol. To determine its stability in vitro, an aliquot of 19 MBq of 68Ga-PSMA-11 was incubated in 1 mL of plasma for 60 min at 37 °C and analyzed using the same protocol.

Image-derived input function
The image-derived input functions (IDIFs) were generated by extracting the median PET activity within a vessel mask at each timeframe. The vessel mask was defined by segmentation of both external iliac arteries clearly visible on Dixon MR registered to PET. The IDIFs were corrected for spill over of PET activity from surrounding tissue to the arteries and for partial volume errors using the approach described in Croteau et al. [15]. Because the partial volume and spill over corrections were estimated based on measurements made using fluorine-18 and highly dependent on the size of the vessel, the vessel mask was restricted to a segment of each iliac artery where the vessels were relatively straight and had the largest diameter (8–9 mm). The IDIFs were then converted to plasma curves using the average plasma-to-blood ratio determined from the arterial blood sampling. In total, IDIFs were derived for 12 subjects. One subject was excluded due to shorter PET scan, which did not provide data enough for fitting of the method, and two subjects were excluded due to excessive motion, which resulted in difficulties to extract the IDIF. The ratio of the area under the curve (AUC) between IDIF and whole blood AIF (AUCr = AUC_IDIF/AUC_AIF) was calculated to verify equivalency of the two input functions.

Kinetic analysis and model validation
Kinetic compartmental modeling assumes that the tracer exchanges between blood and tissue compartments by certain rate constants, which can be determined by a set
of linear, first-order differential equations. Four compartment models were fitted to the data: an irreversible one-tissue compartment model with rate constant $K_1$ (1T1k), a reversible one-tissue compartment model with rate constants $K_1$ and $k_2$ (1T2k), an irreversible two-tissue compartment model with rate constants $K_1$, $k_2$ and $k_3$ (2T3k) and a reversible two-tissue compartment model with rate constants $K_1$, $k_2$, $k_3$ and $k_4$ (2T4k). To account for the contribution from blood activity to the tissue TACs, all models were fitted with and without the fractional blood volume $V_b$. When $V_b$ was accounted for, it was fitted together with the rate constants. The model that best described the lesion uptake was selected based on the Akaike information criterion (AIC) [16, 17]. The net influx rate $K_i = K_1^*k_3/(k_2+k_3)$ was calculated from both the irreversible two-tissue compartment model and from the Patlak graphical method [18]. The Patlak model assumes that when all reversible compartments are in equilibrium with plasma, the Patlak plot becomes linear and the positive slope represents the net influx rate $K_i$. As blood input to the kinetic models, we compared AIF plasma curves and IDIF plasma and whole blood curves. Analysis was done using an in-house MATLAB program (MathWorks, version 2018b).

Simplified protocols and methods for quantification are preferred in routine clinical settings. Therefore, SUV of static images from time-windows 15–30 min, 30–45 min, and 45–60 min were calculated and validated to the net influx rate $K_i$. SUV and $K_i$ were correlated to patient, MR, and histopathological data.

Statistical analysis
Statistical analysis was done using software R (version 3.4.1, R Core Team (2017)) [19]. The level of significance was set to 5%. The distributions of all numerical variables were visually checked and tested for normality and described accordingly by mean ± standard deviation or by median values with 25th and 75th percentiles (Q1 and Q3). Differences between tissue regions and scan time-windows were tested with the Friedman test. Correlations between patient characteristics, MR parameters, SUV, and kinetic modeling parameters, and between $K_i$ from the compartment model and graphical Patlak analysis, were assessed using Spearman correlation analysis (rho). For lesion-based analysis, the most avid lesion (highest SUV in the last 15 min of PET scan) per subject was selected to avoid accounting for dependency between multiple lesions from a single subject. The agreement between $K_i$ using AIF and IDIF was determined using intraclass correlation analysis (ICC3, two-way, mixed model).

Results
The 15 patients included in the study had a median age of 67 years (Q1 = 62.00, Q3 = 72.50) and a median body weight of 75.00 kg (Q1 = 71.00, Q3 = 84.50) [20]. The median serum PSA level was 8.64 ng/mL (Q1 = 5.31, Q3 = 11.77) with a median PSA density of 0.21 ng/mL/g (Q1 = 0.12, Q3 = 0.43). The mean injected activity per body weight was 2.52 ± 0.67 MBq/kg.

One patient had its scan interrupted at 40 min, due to excessive movement. Only lesions identified on both the PET and MR images were considered. One patient was undergoing external beam radiotherapy of the prostate lesion and had no significant $^{68}$Ga-PSMA-11 uptake. This patient was therefore excluded from lesion-based analysis. Of the 14 $^{68}$Ga-PSMA-11 positive patients, 10 had 1 lesion and 4 patients had 2 lesions. In total, 18 lesions were identified with a median lesion size of 1.80 cm (Q1 = 1.10, Q3 = 2.75), of which 17 were located in the prostate and 1 identified as a lymph node metastasis. Gleason scores from previous biopsies were between 6 and 10, with a median Gleason score of 7.00 (Q1 = 7.00, Q3 = 7.00). PI-RADS scores for the lesions located in the prostate were between 2 and 5, with a median PI-RADS score of 5.00 (Q1 = 4.00, Q3 = 5.00). The median ADC was $0.71 \times 10^{-3}$ mm$^2$/s (Q1 = 0.61 × 10$^{-3}$, Q3 = 0.95 × 10$^{-3}$). Figure 1 shows typical $^{68}$Ga-PSMA-11 PET/MR images.

The activity in whole blood and plasma were counted in 83 manual blood samples. The mean plasma-to-blood ratio was 1.62 and was stable during scan time (Fig. 2). The UHPLC analysis demonstrated that $^{68}$Ga-PSMA-11 was stable both in vivo and incubated in plasma in vitro, with a retention time of 5.1 min (Fig. 3). Since $^{68}$Ga-PSMA-11 did not present any radiolabeled metabolites during the 60 min scan time, we could consider the plasma curve as the AIF. Figure 4 shows typical AIF whole blood and plasma curves and IDIF whole blood curve. The mean AUCr between IDIF and AIF curves was 0.84 ± 0.09.

Kinetic analysis and model validation
The tissue TAC’s showed increasing accumulation of $^{68}$Ga-PSMA-11 during scan time in lesions, while for muscle and normal prostate the washout was faster. Based on the AIC analysis, the irreversible two-tissue compartment model without $V_b$ correction provided the best fit to the lesion kinetics. The 2T3k model was preferred in 9/18 lesions, followed by the 2T3k + $V_b$ (3/18), 1T2k (3/18), 2T4k (2/18), and 2T4k + $V_b$ (1/18). The Patlak graphical analysis showed a positive slope from 15 min post-injection (Fig. 5). Due to movement artifacts at the end of the scan, we excluded the last data points in the model and Patlak fits for five patients. In four lesions, the individual rate constants could not be determined with precision, but $K_i$ and $K_i$ as well as Patlak $K_i$ gave robust values. Rate constants $k_3$ and $k_3$ from these lesions were excluded from the median values (Table 1). Both $K_i$, $k_3$, $K_i$ and Patlak $K_i$ were significantly higher in lesions compared to normal prostate and muscle (Table 1). $K_i$ from the compartment
model analysis and Patlak $K_i$ showed strong correlation, with rho of 1.00 in lesion ($p < 0.001$), 0.89 in normal prostate ($p < 0.001$) and 0.93 in muscle ($p < 0.001$).

As to the correlation between kinetic rate constants and patient and MR data, we found significant correlation only between $K_i$ and PSA (rho = 0.62, $p = 0.018$) and between $K_i$ and PSA density (rho = 0.64, $p = 0.015$). The kinetic rate constants did not correlate significantly with Gleason score, PI-RADS, ADC, or lesion size.

The net influx rate constant $K_i$ calculated using IDIF plasma showed excellent agreement with $K_i$ derived using AIF in lesions ($K_i$ ICC = 0.99, $p < 0.001$ and Patlak $K_i$ ICC = 0.98, $p < 0.001$), while the individual rate constants $k_1$ and $k_3$ showed only moderate agreement with $K_i$ and $k_3$ using AIF in lesions ($K_1$ ICC = 0.57, $p = 0.026$, $k_3$ ICC = 0.65, $p = 0.021$). IDIF whole blood resulted in slightly weaker agreement with the AIF plasma-derived rate constants ($K_i$ ICC = 0.89, $p < 0.001$, Patlak $K_i$ ICC = 0.93, $p < 0.001$).

Semi-quantitative analysis
SUV increased significantly with time in lesion and muscle, but not in normal prostate and was significantly higher in lesion compared to normal tissue (Table 2).
Fig. 3 Radiochromatograms from metabolite analysis by UHPLC. Standard solution of $^{68}$Ga-PSMA-11 with a retention time of 5.1 min (a). $^{68}$Ga-PSMA-11 incubated in plasma in vitro, showing a single peak at 5.1 min (b). Patient plasma sample showing a single peak, slightly delayed due to tubing to collect UHPLC fractions (fractions collected every 20 s and subsequently counted in gamma counter) (c).

Fig. 4 Comparison of typical blood sampler plasma (AIF plasma) and whole blood (AIF whole blood) time-activity curves and corresponding image-derived whole blood curve (IDIF whole blood). Inset graph shows the first 10 min of the blood curves.
Table 3 summarizes the SUV correlation analysis. Lesion SUV of all time-windows correlated significantly with lesion $K_i$, where SUV of time-window 30–45 min showed the strongest correlation with a rho of 0.95 ($p < 0.001$). SUV correlated significantly with PSA and PSA density, but not with Gleason score, PI-RADS, ADC, or lesion size.

**Discussion**

The main objectives of this study were to determine the kinetics of the PET ligand $^{68}$Ga-PSMA-11 in primary prostate cancer patients and to validate the use of simplified methods as IDIF and SUV for routine clinical analysis.

Based on the AIC model selection analysis and as indicated by the linear positive Patlak slope, the kinetics of $^{68}$Ga-PSMA-11 during the 60 min scan time could be considered irreversible, as previous studies have indicated [11, 12]. The irreversible kinetics is in line with the process of internalization of PSMA ligands when binding to the specific binding site of the PSMA transmembrane protein. Internalization of PSMA has been shown to be fast and practically irreversible, as the PSMA ligand is recycled in the lysosomes of the cell [21]. In the compartment model, the internalization can be represented by the rate constant $k_3$, which as expected was found to be significantly higher in lesion as compared to normal prostate and muscle. $K_i$, which in the compartment model represents the rate of tracer transport from blood to tissue, was significantly higher in lesions than in normal prostate and muscle, which may reflect the process of angiogenesis in tumor tissue and enhanced tumor tissue permeability [22]. The net influx rate $K_i$—a macroconstant, which incorporates both the transport from blood to tissue and the irreversible trapping of the tracer—was as expected also significantly higher in lesions as compared to normal prostate and muscle. Sachpekidis et al. [11] reported overall greater absolute values in comparison to our rate constant. This could reflect a more advanced prostate cancer study population: the Sachpekidis’ patient cohort had a higher median serum PSA level of 24.1 ng/mL as compared to ours of 8.6 ng/mL, but similar median age and Gleason score. However, more likely this may be the result of omitting plasma-to-blood ratio correction and the result of partial volume effects due to PET-derived blood input. This would underestimate blood activity and consequently overestimate the kinetic rate constants.

We showed that $^{68}$Ga-PSMA-11 is stable in vivo, not necessitating correction for labeled metabolites. Due to the lack of metabolites, PSMA makes an ideal candidate for IDIF, only necessitating the correction for plasma-to-blood ratio. With a plasma-to-blood ratio on average 1.62, this indicates that $^{68}$Ga-PSMA-11 do not penetrate Table 1  Kinetic parameters estimated by the irreversible two-tissue-compartment model

|                | Lesion   | Prostate | Muscle   | $p$ value$^a$ | $p$ value$^b$ |
|----------------|----------|----------|----------|---------------|---------------|
| $K_1$ (mL/min/mL) | 0.136 [0.099, 0.229] | 0.088 [0.078, 0.107] | 0.028 [0.021, 0.033] | 0.006 | 0.001 |
| $k_2$ (mL)     | 0.277 [0.213, 0.484] | 0.239 [0.147, 0.329] | 0.285 [0.184, 0.466] | 0.308 | 0.839 |
| $k_3$ (mL)     | 0.108 [0.057, 0.125] | 0.040 [0.036, 0.056] | 0.040 [0.031, 0.045] | 0.005 | 0.007 |
| $K_i$ (mL)     | 0.036 [0.024, 0.076] | 0.014 [0.010, 0.020] | 0.003 [0.003, 0.003] | 0.001 | 0.001 |
| Patlak $K_i$ (mL) | 0.035 [0.024, 0.096] | 0.012 [0.008, 0.022] | 0.003 [0.003, 0.003] | 0.001 | 0.001 |

Median values with interquartile range [Q1, Q3], $n = 14$ subjects, 18 lesions (median of $k_3$ and $k_2$ from 14 lesions). $p$ values assessed by Wilcoxon test (the most avid lesion per subject selected) comparing lesion with prostate (a) and muscle (b). $K_i$ is the net influx rate calculated from rate constants $k_i k_3/(k_2 + k_3)$ or from the slope of the graphical Patlak analysis.
red blood cells and remains in plasma, giving a plasma-to-blood ratio ($R_{P/B}$) depending only on hematocrit (HCT) following the equation $R_{P/B} = 1/(1–HCT)$. A $R_{P/B}$ of 1.62 would equal a HCT factor of 38%, which is within the normal range of HCT for men [23]. As the plasma-to-blood ratio depends only on HCT, the value of 1.62 should be stable between subjects, not necessitating arterial blood sampling in future IDIF studies.

Although IDIF simplifies the acquisition protocol for quantification considerably as compared to blood sampling, for routine clinical settings there is a need for even simpler quantification methods. Here, we showed that SUV of all time-windows correlated significantly with $K_i$ for routine clinical settings there is a need for even quantification considerably as compared to blood sampling. We report significant correlation between PET-derived input function as compared to our studies [11, 12]. Again, this might reflect the less accurate PET-derived input function as compared to our arterial input function. We report significant correlation between PSA and SUV (rho = 0.65), similar to the rho of 0.60 reported by Sachpekidis et al. [11], but also a significant correlation between PSA and $K_i$ independently of Sachpekidis et al. who did not find a significant correlation between the kinetic parameters and PSA. Our data did not, however, present a significant correlation between SUV and Gleason score, differently from Sachpekidis’ study, which reported a weak but significant correlation (rho = 0.33, $p < 0.05$). The lack of correlation between PET and MR parameters might be due to our small patient sample.

The strong correlation between $K_i$ and SUV demonstrates that SUV can be used to quantify $^{68}$Ga-PSMA-11 uptake in primary prostate cancer patients. A similar study of the kinetics of $[^{18}F]$fluorocholine concluded that SUV could not be used to quantify $[^{18}F]$fluorocholine uptake due to poor correlation between SUV and $K_i$ [24], demonstrating the importance of undertaking quantitative studies to validate simplified semi-quantitative methods.

Interestingly, a comparison of the SUV between time-windows 15–30 min, 30–45 min, and 45–60 min showed that the strongest correlation between $K_i$ and SUV was not seen for the latest time-window, but rather the 30–45 min time-window. This result contrasts from current guidelines and publications, where a standard uptake time of around 60 min, with an acceptable range of 50 and 100 min, is recommended [11, 25–27]. A preliminary analysis of the optimal time-window for lesion visualization showed in agreement with the correlation analysis that the lesions were more easily outlined in early timeframes than in late, mainly due to lower bladder activity in early timeframes. Future studies are needed to determine the optimal time-window for image reporting and quantification.

### Conclusions

The kinetics of $^{68}$Ga-PSMA-11 are best described by an irreversible two-tissue compartment model. $^{68}$Ga-PSMA-11 is stable in vivo, which excludes the need for metabolite correction. The net influx rate $K_i$, estimated using an MR-guided image-derived input function showed excellent agreement with the arterial input function $K_i$. Image-derived blood can therefore be used as an alternative to arterial blood sampling in kinetic modeling studies. SUV correlated significantly with $K_i$ and can be used in routine clinical settings to quantify $^{68}$Ga-PSMA-11 uptake.

### Table 2

| SUV   | Lesion      | Prostate    | Muscle     | $p$ value$^a$ |
|-------|-------------|-------------|------------|---------------|
| 15–30 min | 4.95 [3.50, 6.94] | 2.48 [2.05, 2.81] | 0.54 [0.53, 0.56] |               |
| 30–45 min | 5.63 [4.04, 9.80] | 2.61 [2.15, 3.12] | 0.56 [0.52, 0.62] |               |
| 45–60 min | 5.98 [4.84, 11.72] | 2.94 [2.28, 3.49] | 0.61 [0.56, 0.72] | $<0.001$      |

Median values with interquartile range [Q1, Q3], $n = 14$ subjects, 18 lesions. $p$ values assessed by Friedman test (the most avid lesion per subject selected) comparing regions (a) and time-windows (b).

### Table 3

| SUV     | $K_i$ Rho | PSA Rho | PSA density Rho | $p$ value |
|---------|-----------|---------|-----------------|-----------|
| 15–30 min | 0.83 < 0.001 | 0.52 0.056 | 0.55 0.041 |
| 30–45 min | 0.95 < 0.001 | 0.64 0.014 | 0.61 0.019 |
| 45–60 min | 0.88 < 0.001 | 0.65 0.015 | 0.67 0.012 |

Spearman correlation rho with corresponding $p$ value. $n = 14$, the most avid lesion per subject selected.

### Abbreviations

- $1T1k$: Irreversible one-tissue compartment model
- $1T2k$: Reversible one-tissue compartment model
- $2T4k$: Reversible two-tissue compartment model
- $2T3k$: Irreversible two-tissue compartment model
- $1T1k$: Irreversible one-tissue compartment model
- $1T2k$: Reversible one-tissue compartment model
- $2T4k$: Reversible two-tissue compartment model
- AIC: Akaike information criterion
- AIF: Arterial input function
- ADC: Apparent diffusion compartment model
- 1T1k: Irreversible one-tissue compartment model
- 1T2k: Reversible one-tissue compartment model
- HASTE: Half-Fourier single shot turbo spin echo
- HCT: Hematocrit
- IDIF: Image-derived input function
- MR: Magnetic resonance
- OSEM: Ordered-subsets expectation maximization
- PET: Positron emission tomography
- PI-RADS: Prostate Imaging Reporting and Data System
- PSA: Prostate-specific antigen
- PSMA: Prostate-specific membrane antigen
- PSMA-11: Glu-urea-Lys(Ahx)-HBED-CC
- Q1: 25th percentile
- Q3: 75th percentile
percentile; ROI: Region-of-interest; \( R_{18F} \): Plasma-to-blood ratio; SUV: Standardized uptake value; TAC: Time-activity curve; TFA: Trifluoroacetic acid; UHPLC: Ultra-high-pressure liquid chromatography; \( V_f \): Fractional blood volume; VBE: Volumetric interpolated breath-hold examination; VOI: Volume-of-interest

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Authors’ contributions

AR designed the study, acquired and analyzed all data, and wrote the manuscript. GCN contributed to the design of the study, acquired and analyzed PET/MR data, and contributed to the writing of the manuscript. UA contributed to the design of the study, acquired and analyzed IDIF data, and contributed to the writing of the manuscript. LC acquired and analyzed blood data and revised the manuscript. RHB designed the study, supervised the manuscript. GCL contributed to the design of the study, was responsible for analyzing blood data, and contributed to the writing of the manuscript. LLF analyzed PET/MR data and revised the manuscript. MFB contributed to the design of the study, acquired and analyzed IDIF data, and contributed to the writing of the manuscript. ACM contributed to the design of the study, acquired and analyzed all data, and wrote the manuscript. MLC analyzed PET/MR data and contributed to the writing of the manuscript. LA contributed to the design of the study, acquired and analyzed blood data, and contributed to the writing of the manuscript. MLI analyzed PET/MR data and contributed to the writing of the manuscript. VIT designed the study, supervised the manuscript. GJC is supported by Siemens-MITACS Fellowship Canada.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the figshare repository, https://doi.org/10.6084/m9.figshare.10265825.

Ethics approval and consent to participate

The study was approved by the ethics committee of Hospital Israelita Albert Einstein (reference number 58175716.0.0000.0071) and informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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