THE ACCURACY OF KIDNEY'S TIA CALCULATED FOR THREE TIME POINTS BIOKINETIC DATA OF [^{177}LU]LU-DOTATATE USING MONO-EXPONENTIAL FUNCTION

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Abstract *This study evaluates the accuracy of time-integrated activities (TIAs) using different sampling schedules of biokinetic data for [^{177}Lu]Lu-DOTATATE in kidneys, focusing on three-time points (3TPs) schedules. The biokinetic data were obtained from PMID33443063. The data were collected from six patients using SPECT/CT measurements at four-time points (4TPs) with various combinations of the following time points: T1=(4.2±0.5), T2=(34.9±11.6), T3=(99.8±1.5), T4=(124.3±3.2), and T5=(167.4±19.7) h post-injection. A mono-exponential function was fitted to 4TPs data to calculate reference TIAs (rTIAs). Parameters from this function were refitted to 10 combinations of three data sets to derive three-time points TIAs (3TPTIAs). The root-mean-square error (RMSE) of relative deviation (RD) between 3TPTIAs and rTIAs was analyzed. The sampling schedule for the 3TPs with the lowest RMSE, at 1.19%, was the combination of T1, T2, and T4 hours. On the other hand, all 3TPs fitting combinations excluding T1 were identified as having the highest RMSE, at 17.15%. The best combination of 3TPs was achieved by including T1, T2, and T4. It is important to include T1 when using the mono-exponential function and 3TPs data, as its presence impacts the accuracy of kidney dosimetry for [^{177}Lu]Lu-DOTATATE therapy. Selecting an optimal schedule of 3TPs enhances kidney dosimetry accuracy.*

INTRODUCTION

In Peptide Receptor Radionuclide Therapy (PRRT) using [^{177}Lu]Lu-DOTATATE (1), the kidneys are considered as organs at risk (2). Kidney dosimetry is desirable for therapy monitoring (3,4). Kidney dosimetry allows healthcare practitioners to proactively assess and manage the toxicity of the kidneys, optimizing treatment outcomes while mitigating the risk of adverse effects associated with elevated doses to this vital organ (3,5).

According to the Committee on Medical Internal Radiation Dose (MIRD), determining the time-integrated activities (TIAs) is important for calculating the absorbed dose. Multiple kidney imaging scans are necessary to calculate the TIAs, ideally with a minimum of three-time points for single-photon emission computed tomography /computed tomography (SPECT/CT) acquisition, as recommended in the literature (6). However, achieving precise TIAs is not solely dependent on the quantity of SPECT/CT acquisitions but also relies on the selection of sampling times (6–9). Therefore, standardizing the sampling times for activity measurements becomes imperative to ensure accuracy in TIAs.

The MIRD pamphlet No. 23 (10) stated that the quantity of time point measurements relies on the number of exponential terms present in the TIAs of each source volume. With a limited number of time points (three time points), many practitioners use the mono-exponential function to the whole body in which uptake is instantaneous to model the clearance of radiopharmaceuticals (11–13). In this study, we aim to analyze the accuracy of TIAs calculated using different sampling schedules of biokinetic data for [^{177}Lu]Lu-DOTATATE in the kidneys based on the mono-exponential function.

METHODOLOGY

Patient Imaging

The biokinetic data of [^{177}Lu]Lu-DOTATATE in both the left and right kidneys were obtained from the literature PMID33443063 (14). Six patients with NETs underwent multiple time point SPECT/CT imaging after receiving one cycle of standard treatment with [^{177}Lu]Lu-DOTATATE PRRT at the University of Michigan Medical Center between August 2018 to March 2020. Approval was obtained from the Institutional Review Board, and all participating patients provided written informed consent. The patients were given an intravenous activity of 7255±157 MBq of [^{177}Lu]Lu-DOTATATE. Consecutive imaging was performed using a Siemens Intevo Bold SPECT/CT system and imaged at T1 = (4.2 ± 0.4), T2 = (38.2 ± 11.3), T3 = (99.6 ± 1.5), T4 = (124.2 ± 3.1), and T5 = (168.0 ± 16.1) hour after injection. Each patient we used had four biokinetic data measurements for both the right and left kidney with different combinations of time points. This data can be found in Supplemental Table 1 of the reference (14).

Three time point combinations

In this study, we investigated ten different samplings of three-time points (3TPs) combinations derived from an available dataset. The details of these 3TPs combinations can be found in Table 1, categorizing patients according to their specific combinations of time points. To identify a time point influencing 3TPs performance when using a mono-exponential function, we systematically grouped combinations as summarized in Table 2.

Study Workflow

The parameters of the mono-exponential function in Eq.1 were individually fitted to the biokinetic data of six patients

$$A(t) = A_1 e^{(\lambda_1+\lambda_{phys})t} \quad (1)$$

where $A(t)$ is a function with two parameters, A_1 is activity pre-factor in the kidneys, λ_1 describe the biological clearance rate of radiopharmaceuticals and λ_{phys} is the physical decay constant of the radionuclide calculated from the half-life of ^{177}Lu ($T_{1/2}$ = 6.6643 days) (15). The estimated parameters were constrained to positive values. Figure 1 shows the workflow of this study. The 4TPs and 3TPs fitting were performed in the SAAM II software application for Kinetic Analysis version 2.1 (16). The computational settings employed for all fittings including the Rosenbrock algorithm, a convergence criterion of 10^{-4}, a data-based, relative-based variance model, and proportional error model, as described in the literature (17–19). The Goodness-of-Fit (GoF) evaluation was assumed to be accepted based on a visual inspection of the fitted graph and the coefficient of variation (CV) value. A good visual fit represents a fitted curve passing through the data or closely aligning with data points and having random trends. The CV value was obtained by comparing the estimated parameter values obtained and the standard error caused by the parameter estimates. The CV value tolerance limit is less than 50% (20,21).

Table 1. List of 3TPs combination. Each combination is denoted by codes C1 through C10

3TPs Combination Code	Time Points	Patient(s)
C1	T1, T2, T3	P1, P4, P5
C2	T1, T3, T4	P1, P2, P3
C3	T2, T3, T4	P1
C4	T1, T2, T4	P1, P6
C5	T1, T3, T5	P2, P3, P4, P5
C6	T1, T4, T5	P2, P3, P6
C7	T3, T4, T5	P2, P3
C8	T1, T2, T5	P4, P5, P6
C9	T2, T3, T5	P4, P5
C10	T2, T4, T5	P6

Table 2. List of combinations of excluded time points

Excluded Time Point	3TPs Combinations
T1 Excluded	C3, C7, C9, C10
T2 Excluded	C2, C5, C6, C7
T3 Excluded	C4, C6, C8, C10
T4 Excluded	C1, C5, C8, C9
T5 Excluded	C1, C2, C3, C4

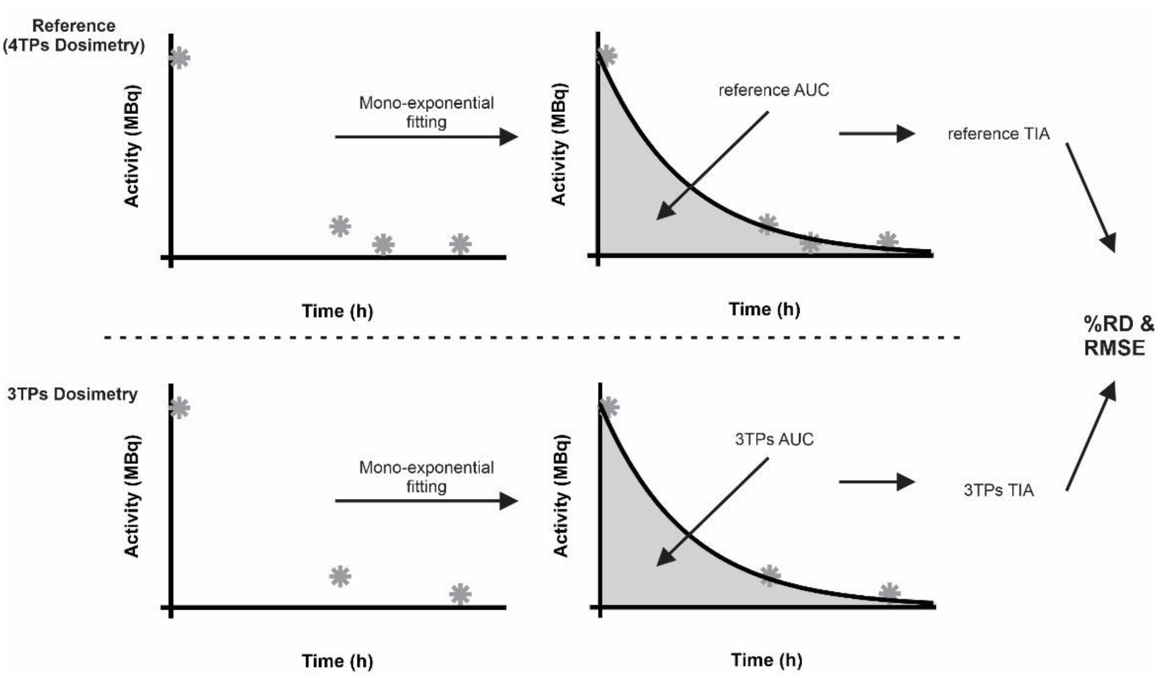

Figure 1. Schematic overview of the workflow. The 3TPs dosimetry comprises all of the combination of 3TPs compared to the reference TIAs using four time points. The RMSE was calculated from the mean and SD of the relative deviation percentage.

The TIAs, defined as the area under the curve integrated from injection time zero to infinity, were computed for both 4TPs and 3TPs approaches. Employing the analytical solution in Eq. (2), the reference TIAs (rTIAs) were derived from 4TPs. Simultaneously, the three-time points TIAs (3TPTIAs) were calculated based on the three-time points combination.

$$TIA_i = \int_0^\infty A_{1_i} e^{\left(\lambda_{1_i}+\lambda_{phys}\right)t} dt = \frac{A_{1_i}}{\lambda_{1_i}+\lambda_{phys}} \qquad (2)$$

where i is the TIA of 4TPs or 3TPs approach. The standard deviation of rTIAs and 3TPTIAs was calculated using error propagation of the uncertainty of the estimated parameters (22). The performance of 3TPTIAs was compared with the rTIAs by calculating the percentage of relative deviation (RD) and root-mean-square errors (RMSEs) according to Equation 3 and Equation 4, respectively (23).

$$\%RD_j = \frac{3TPTIA_j - rTIAs}{rTIAs} \times 100\% \qquad (3)$$

$$RMSE_j = \sqrt{\left(SD_{RD_j}\right)^2 + \left(Mean_{RD_j}\right)^2} \qquad (4)$$

where RD_j is the relative deviation of the 3TPs combination of j -th, $\mathrm{3TPTIA}_j$ are the TIAs calculated using 3TPs combination of j-th, rTIAs are the reference TIAs calculated from four-time point data, RMSE_j is the root-mean-square-errors of the time point combination of j-th, and SD_{RD_j} and $Mean_{RD_j}$ are the standard deviation and mean of RD_j of the time point combination of j-th.

RESULTS AND DISCUSSION

Dosimetry in PRRT is necessary to monitor the therapy's impact on the kidneys and optimize outcomes while minimizing adverse effects. MIRD Pamphlet No. 23 stated that the exponential terms used for describing radiopharmaceutical clearance rely on the number of measurements (10). The use of 3TPs for accurate kidney dosimetry has been widely recommended in MIRD Pamphlet No.16 (6). Using 3TPs, many users frequently used a mono-exponential function to fit the data (24–28). In this study, we evaluated the accuracy of TIAs using the mono-exponential function for [^{177}Lu]Lu-DOTATATE in the kidneys with various sampling schedules of 3TPs.

Visual inspection and CV analysis indicated good fits on nearly all fittings. The estimated parameters show the CV value below the 50% threshold for most combinations, except for one combination (P2 in combination C7) which involves T3, T4, and T5. The combination of T3, T4, and T5 did not meet the criteria for a good fit. It is important to note that the CV values for parameters A_1 and λ_1 associated with P2 in combination C7 are higher than 50%. Nevertheless, P3 in combination C7 is still included in the investigation.

The results of the different combinations of 3TPs were represented by the RMSE values in Table 3. Among these combinations, nine of 3TPs combinations had RMSE below 12%, namely combination C1, C2, C3, C4, C5, C6, C8, C9, and C10. Notably, combination C4 exhibited the lowest RMSE, which combines T1, T2, and T4 at 1.20. It indicates that the configuration of time point C4 makes the TIAs accurate and has a reliable prediction compared to all the other combinations considered in this study. For example, in the P1-Left Kidney in Figure 2(a), there were no significant differences visually between the reference curve and the 3TPs curve in combination C4. In contrast, the C7 had the highest RMSE at 28.60, as P2 did not pass the goodness-of-fit test. P2-Left Kidney (Figure 2(b)) had significant visual differences between the reference and the 3TPs curves. This difference may arise from the necessity of including an early time point (1d or 2d post-injection), as omitting early time points could result in inaccurate TIAs when using a mono-exponential function and 3TPs. Figure 3 shows the highest RMSE when T1 was excluded. In the case of 3TPs fitting use a mono-exponential function, where uptake occurs very quickly, and measurements cannot detect it, the early time point becomes very important.

Table 3. The rank and RMSE of 3TPs Combination

3TP Combination Code	Time Points	RMSE	Rank
C1	T1, T2, T3	6.64	7
C2	T1, T3, T4	1.87	3
C3	T2, T3, T4	1.89	4
C4	T1, T2, T4	1.20	1
C5	T1, T3, T5	9.26	8
C6	T1, T4, T5	2.76	6
C7	T3, T4, T5	28.60	10
C8	T1, T2, T5	1.23	2
C9	T2, T3, T5	11.99	9
C10	T2, T4, T5	2.25	5

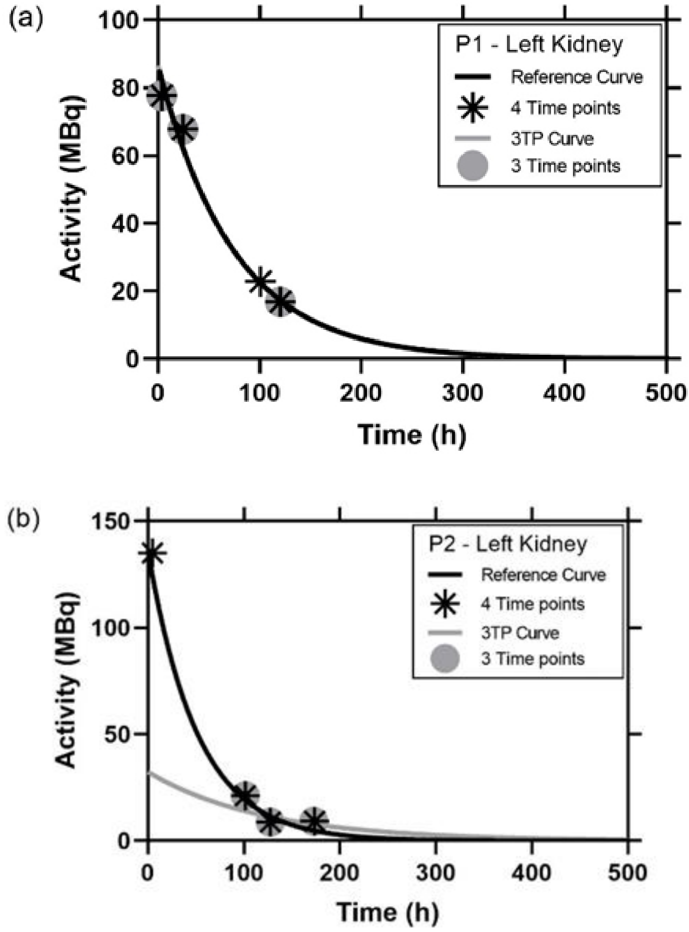

Figure 2. Time activity curve (TAC) of 4TPs as a reference compared to TAC of 3TPs. (a) The curve denotes TAC for the left kidney of P1 based on 4TPs and 3TPs of C4. (b) The curve denotes TAC for the right kidney of P2 based on 4TPs and 3TPs of C7.

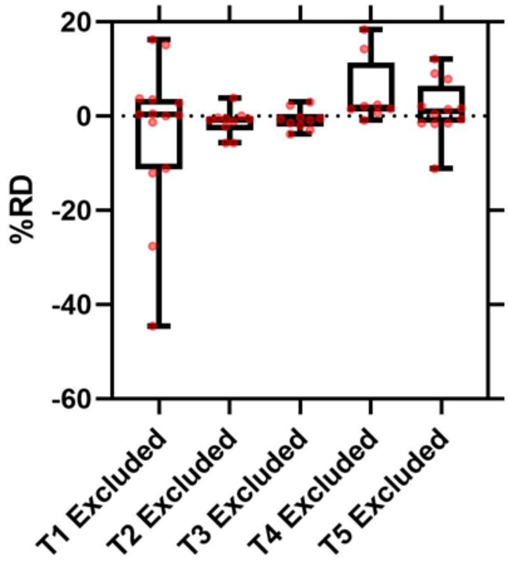

Figure 3. The %RD boxplot of combination 3TPTIAs in which a specific time point was excluded. The red dots show the RD of TIA between rTIAs and 3TPTIAs.

According to Eq. (2), TIA is calculated using the fitted parameters A_1 and λ_1 . These parameters rely on the input data, specifically the radioactivity levels of the radiopharmaceutical in the kidney (29). The radioactivity levels over time in the kidney may vary due to intraindividual variability. Differences in intraindividual variability result in slope changes in the fitted curve, which affects how the mathematical model describes the pharmacokinetics of [^{177}Lu]Lu-DOTATATE, leading to differences in TIA when time sampling varies. For example, it can be shown in Figure 4 that there was a large difference in the RMSE between C5 and C8, considering the only variation is the time point, with C5 at T3 and C8 at T2. On the other hand, the RMSE between C2 and C4 was not significantly different, despite having the same variations with C5 and C8 (different time points at T3 for C2 and at T2 for C4). The notable difference between C5 and C8 arose from the RD between the rTIAs and the 3TPTIAs for patient 2, while other patients exhibit relatively low RD. Regarding the pharmacokinetics [^{177}Lu]Lu-DOTATATE of P2 in the combination C5, the fitted parameter λ_1 for patient 2's tended to shift (to the right) the slope of the curve, resulting in an increased TIA. In contrast, for combinations C2 and C4, all patients demonstrated relatively low RD with relatively similar pharmacokinetics of [^{177}Lu]Lu-DOTATATE, which led to a lower RMSE.

Based on Table 3, the combination C1 shows a greater RMSE than the combination C2, C3, C4, C6, C8, and C9 because the C1 combination does not have a late time point. The absence of late time points in the 3TPs when using a mono-exponential function can result in inaccurate TIAs. Figure 3 also shows the high RMSE when T4 and T5 were excluded. This finding is in good agreement with the kinds of literature emphasizing the role of late time points in accurately determining TIAs (30), particularly for radiopharmaceuticals with long physical half-lives such as ^{177}Lu (28,31)

The combination of early and late 3TPs when using a mono-exponential function affects TIAs accuracy for the investigated patient population and [^{177}Lu]Lu-DOTATATE. This is following research conducted by Freedman et al. that having an early and a late time point when using a mono-exponential function, can produce a reliable TIAs (13). It is crucial for healthcare professionals to consider the presence of both early and late time points when performing TIAs calculations using 3TPs.

We recognize that our limited study is primarily related to the number of biokinetic data available. Therefore, it is important that our presented results may only be considered applicable to the investigated patient population and [^{177}Lu]Lu-DOTATATE. To enhance the validity and generalizability of these findings, future research should focus on collecting more comprehensive biokinetic data involving a larger sample size.

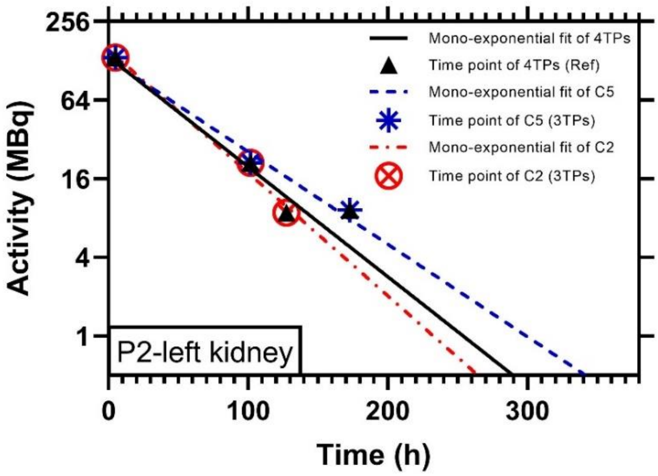

Figure 4. The slope of the combination C5 fitted curve for the P2-left kidney (blue line) shifted to the right of the fitted curve of 4TPs (black-line as reference). This shift led to 3TPTIAs having higher TIAs than rTIAs with RD of 14.3%. In contrast for C2 of the P2-left kidney, the slope of the combination C2 fitted curve (red line) moved slightly to the left of the reference. This shift was not significantly different from the reference, resulting in relatively similar TIAs with RD of 1.4%.

CONCLUSION

This study demonstrates that the combination of T1 = (4.2 ± 0.4), T2 = (38.2 ± 11.3), and T4 = (124.2 ± 3.1) h yields the most accurate 3TPs combination for the investigated patient population and radiopharmaceuticals. The inclusion of both early and late in 3TPs is crucial for accurately describing TIAs when using the mono-exponential function. However, further investigation using a larger biokinetic dataset is required to enhance the validity and generalizability of our findings.

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