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Methodological Evaluation of Renal Time-integrated Activity Coefficient Calculated using Trapezoidal Method and Non-linear Mixed-Effects Modeling in [^{177}Lu]Lu-DOTA-TATE Therapy

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ABSTRACT

This study aimed to compare renal Time-Integrated Activity Coefficients (TIACs) in [^{177}Lu]Lu-DOTA-TATE therapy calculated using the trapezoidal method and Non-Linear Mixed-Effects (NLME) modeling. Renal biokinetic data of [^{177}Lu]Lu-DOTA-TATE were collected from ten patients with neuroendocrine tumors. SPECT/CT imaging was performed between days 1 and 7 after-injection. The full trapezoidal method and the trapezoidal method combined with monoexponential decay from last time point was implemented in R version 4.5. In addition, the TIACs calculated using a bi-exponential function derived from NLME modeling implemented in NONMEM software version 7.6.0 was also analyzed. TIACs derived from bi-exponential fit function with NLME modeling were considered as reference TIACs (rTIACs). The performance of trapezoidal method in estimating the TIACs was evaluated using Relative Deviations (RDs) from the rTIACs. Full trapezoidal method systematically underestimated the rTIACs with mean of RD of -17% while the trapezoidal method with monoexponential decay from the last time point systematically overestimated the rTIACs with mean RD of 30%. Therefore, the implementation of appropriate model-based fit functions is recommended, as relying on an inadequate method may result in systematic over- or underestimation of the TIAC values.

INTRODUCTION

Peptide Receptor Radionuclide Therapy (PRRT) using [^{177}Lu]Lu-DOTA-TATE has been widely used for patients with metastatic somatostatin receptor-positive Neuroendocrine Tumors (NETs) [1,2]. Accurate renal dosimetry in [^{177}Lu]Lu-DOTA-TATE therapy remains essential because the kidneys act as the dose-limiting organ due to tubular reabsorption of the radiopeptide [3,4]. The state of the art in dosimetry has evolved significantly in recent years. Methodologies in the literature range from the simple trapezoidal method [5-7] to comprehensive whole-body physiologically based pharmacokinetic modeling [3,8,9]. However, regardless of the complexity of the overarching model, the reliance on the simple trapezoidal rule can contribute to significant differences in absorbed dose estimation [10].

The accurate estimation of Time-Integrated Activity Coefficients (TIACs) is highly desirable in Molecular Radiotherapy (MRT). TIACs, known formerly as residence times, represent the cumulative number of disintegrations in a source region per unit of administered activity, reflecting the average time the radiopharmaceutical remains in the source organ. They serve as the input in the Medical Internal Radiation Dose (MIRD) formalism to calculate the absorbed dose [5,11]. Ensuring high accuracy in TIAC estimation is critical for evaluating both the safety and therapeutic efficacy of MRT protocols [12-14]. The simplest method for estimating TIACs is trapezoidal integration [5].

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This numerical integration technique approximates the area under the time-activity curve by connecting consecutive data points with linear splines and summing the areas of the resulting trapezoids [6]. Due to its computational simplicity, it is still utilized in recent studies such as the evaluation of [^{177}Lu]Lu-PSMA-617 tumor dosimetry by Peters et al. [7].

An alternative and widely accepted method for approximating TIACs involves fitting the sum-of-exponentials function to the biokinetic data [5,6]. Among the various functional forms available [15], the bi-exponential function with Non-Linear Mixed-Effects (NLME) modeling is utilized to describe the uptake and clearance of [^{177}Lu]Lu-DOTA-TATE [16]. Unlike the trapezoidal method [6,7], NLME modeling incorporates both fixed-effects (representing typical values of the parameters) and random effects (accounting for inter-individual variability). This simultaneous analysis of all cohort data significantly increases the ratio of available data to fitted parameters [17], maintaining estimation accuracy even with sparse sampling [18,19]. Furthermore, compared to the trapezoidal method, NLME modeling allows for more robust interpolation between data points and plausible extrapolation beyond the measurement time point [6].

Despite the widespread study of both trapezoidal integration [7] and sum-of-exponentials functions with NLME models [17,20], there is currently a lack of literature specifically evaluating and comparing the performance of these two methods. To date, no comprehensive study has addressed how these different mathematical approaches impact the resulting TIAC values. To address this gap, this study utilizes the renal biokinetic dataset previously published by Devasia et al. (2021) [16]. This dataset was selected because the previous study successfully demonstrated that the bi-exponential function with NLME modeling provides an acceptable fit for these specific data. Consequently, utilizing this established dataset and fit function serves as a validated reference for evaluating the accuracy of the trapezoidal method. It is important to note that this study does not aim to reproduce the NLME modeling proposed by Devasia et al., which investigated the possibility of reduced time points in clinical dosimetry [16], but to evaluate the difference of estimated TIACs derived from the trapezoidal method and the bi-exponential function with NLME modeling using the same biokinetic dataset. Consequently, the primary focus of this study is a methodological comparison of mathematical modeling for estimating the TIACs, rather than the generation of new clinical data or biological interpretation. Therefore, this study aims to provide a performance evaluation of TIACs derived from the trapezoidal rule and bi-exponential fit functions, establishing an understanding of their respective accuracies in MRT dosimetry.

MATERIALS AND METHODS

Biokinetic data

The renal biokinetic data of [^{177}Lu]Lu-DOTA-TATE were obtained from a previously published study by Devasia et al. (PMID: 33443063) [16]. The dataset consists of ten patients with NETs treated at the University of Michigan Medical Center who received the injected activity of (6.9 ± 1.1) GBq. SPECT/CT imaging was performed on all patients between day 1 and day 7 (at ~ 3 h, 24 h, 100 h, and 167 h) following radiopharmaceutical injection. Eight patients underwent imaging at four time points, while the remaining two had only two imaging time points, performed at ~4 h and ~120 h after injection. The comprehensive description of the image acquisition and accumulation profile in the kidneys was described in the previously published study [16].

Trapezoidal and combined trapezoidal with monoexponential function

Trapezoidal rule basically is a method connecting the measured data points with the linear line (polygon approach or linear spline) [6]. Let n be the number of measured time points so that the biokinetic measurement is performed at time $t_{0=0}, t_1, \cdots, t_n$ and the measured biokinetic data were $y_{0=0}, y_1, \cdots, y_n$. Therefore, the TIACs in the trapezoidal method can be approximated using trapezoidal integration in Eq. (1).

$$\mathrm{TIACs} = \frac{1}{\mathrm{A_{inj}}} \sum_{i=1}^{n} \frac{(t_i - t_{i-1}) \cdot (y_i - y_{i-1})}{2} \qquad (1)$$

with A_{inj} is injected activity. The estimation of TIACs in Eq. (1) was integrated only up to the last measured time point (method 1). To account for the decay up to infinity, the physical decay was added from the last measured time point to infinity as the extrapolation method in the combined trapezoidal with monoexponential function method (method 2). The TIACs estimations in these methods are performed using R version 4.5 [21].

Non-linear mixed-effects modeling

NLME modeling consists of a structural and a statistical model [18]. The structural model refers to

the mathematical function employed to describe the trend of the measured data. In contrast, the statistical model is employed to account for inter-individual variability within the population and residual variability, which represents the difference between model prediction and observed biokinetic data.

The structural model in this study is the bi-exponential fit function, which is assumed as the reference fit function as performed in the previous study [16]. The bi-exponential function is expressed in Eq. (2).

$$A(t) = \frac{k_e \times k_a}{c(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right) \qquad (2)$$

where k_e denotes the effective elimination (or decay) rate of [^{177}Lu]Lu-DOTA-TATE in the kidneys; k_a represents the uptake rate in the kidneys; and c is a scaling parameter [16]. The individual parameter was estimated using an exponential error model, as it ensures positive parameters and is commonly used to describe the pharmacokinetic parameters [18,22,23]. The individual parameter is expressed in Eq. (3).

$$\theta_{ki} = \theta_k e^{\eta_{ki}} \qquad (3)$$

with θ_{ki} is parameter k for i^{th} individual, θ_k represents the fixed effects of the parameter k and η_{ki} denotes the individual-specific deviation of the parameter from the θ_k. The value of η_{ki} is in log-domain and assumed to be normally distributed with a mean of zero and a variance of ω^2. The residual variability, which describes the discrepancy between model prediction and observed biokinetic data, is described using a proportional error model [9,15] in Eq. (4).

$$Y_{\text{obs},i} = Y_{\text{pred},i}(1 + a \times \varepsilon) \qquad (4)$$

In Eq. (4), the value of a denotes the fractional standard deviation, and ε is a normally distributed error with a mean of zero and a variance of one.

The NLME modeling was performed in NONMEM software version 7.6.0 [24-26]. During the development of models, all parameters were assumed to have random effects. The applied goodness-of-fit criteria were visual inspection of the biokinetic curves, relative standard errors (RSEs) of the fitted parameters < 50%, and the absolute value of the off-diagonal in the correlation matrix <0.8 [27-29].

TIAC in this method was calculated analytically by integrating the time activity curve, Eq. (2), from time zero to infinity, as expressed in Eq. (5).

$$\text{TIAC} = \frac{1}{c} \qquad (5)$$

Performance metric

In this study, the TIACs derived from the bi-exponential fit function, Eq. (5), was used as the reference TIACs (rTIACs) [16]. The performance of Trapezoidal method 1 and Trapezoidal combined with monoexponential decay method 2 was evaluated using the Relative Deviations (RDs) metric, which is expressed in Eq. (6).

$$\text{RD}_\text{i} = \frac{\text{eTIAC}_\text{i} - \text{rTIAC}_\text{i}}{\text{rTIAC}_\text{i}} \qquad (6)$$

with RD_i represents the RD for the individual i; eTIAC_i denotes the estimated TIAC from both method 1 and method 2.

RESULTS AND DISCUSSION

Figure 1 illustrates the biokinetic curves for the left kidney of patient 8. The biokinetic curves for the remaining kidneys and patients are similar to those shown in Fig. 1. No goodness-of-fit criteria were applied to Method 1 or Method 2, as these methods interpolate data using linear splines, ensuring the function passes directly through each measured data point. In contrast, the bi-exponential fit function fitted with NLME modeling shows an adequate biokinetic curve in describing the data (Fig. 1), yielding a maximum RSE of 40% and a maximum absolute value of the off-diagonal elements in the correlation matrix of 0.53. Therefore, the bi-exponential fit function satisfied the predefined goodness-of-fit criteria [27-29].

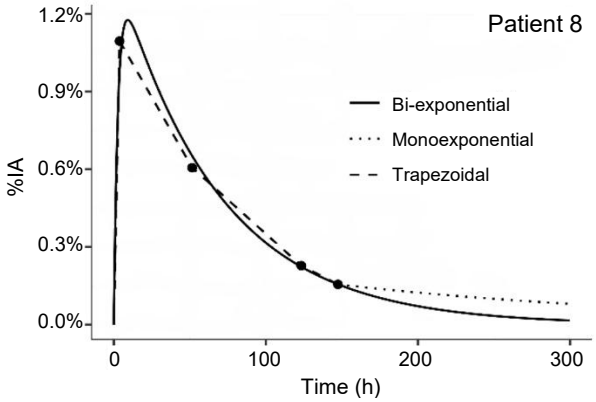

Fig. 1. Biokinetic curve of the left kidney for patient 8, showing median Time-Integrated Activity (TIAC) values. The curve illustrates the comparison between the bi-exponential fit function, the trapezoidal method, and the combined trapezoidal method with a monoexponential tail.
Note: The analysis in this study was performed on a dataset of 20 kidneys from 10 patients within the dataset in this study.

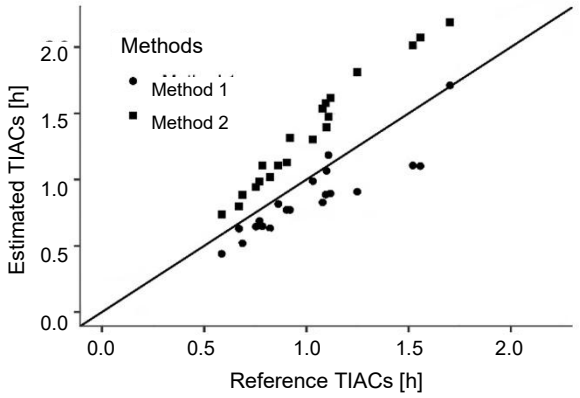

Fig. 2. Comparison of TIACs estimated by the full trapezoidal method (Method 1, circles) and the trapezoidal method with monoexponential extension (Method 2, squares) versus the reference rTIACs derived from NLME modeling. The solid line represents the line of identity ($y = x$). Data points falling below the line indicate underestimation, while points above the line indicate overestimation, illustrating the systematic deviations across the full dataset of 20 kidneys.

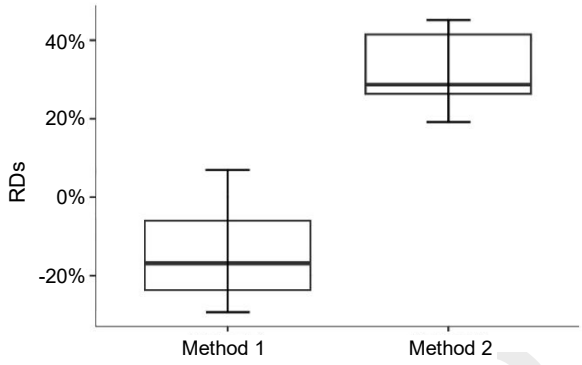

Fig. 3. Boxplot of Relative Deviations (RDs) for estimated Time-Integrated Activity Coefficients (eTIACs). RDs were calculated for both the trapezoidal method and the trapezoidal method with a mono-exponential function, relative to the reference TIAC (rTIAC) derived from a bi-exponential fit using nonlinear mixed-effects (NLME) modeling. The analyses are performed for all patients (20 kidneys) in this study.

To visualize the agreement between the eTIACs and the rTIACs across the full cohort, the eTIACs were plotted against the rTIACs (Fig. 2). The scatter plot reveals a distinct separation relative to the line of identity ($y = x$). The full trapezoidal method (Method 1) consistently yielded values below the identity line, indicating a systematic underestimation. In contrast, the trapezoidal method with monoexponential extension (Method 2) resulted in values largely above the identity line, indicative of overestimation. To quantify the magnitude of these errors, the RDs were calculated.

Figure 3 illustrates the RDs of trapezoidal method 1 and combined trapezoidal-monoexponential methods 2 relative to the rTIACs derived from the full cohort of ten patients (20 kidneys) analyzed in this study. Method 1 yielded a median RD of -17%, whereas method 2 resulted in a median RD of 29%. These findings suggest that the trapezoidal method tends to underestimate the rTIACs, while the addition of a monoexponential function leads to an overestimation.

The trapezoidal method inherently underestimates the "true" TIAC because it only integrates the biokinetic curve up to the final measurement point, whereas the rTIAC accounts for the area from time zero to infinity. This systematic negative bias occurs because the method neglects the terminal clearance phase. Despite this limitation, the trapezoidal method is typically employed when a monoexponential fit is inadequate, ($R^2 < 0.7$) as demonstrated by Peters et al. (2023) [7]. One should therefore account for this underestimation when interpreting results derived solely from the trapezoidal method.

The addition of a physical decay tail from the last measurement point led to an overestimation of the biokinetic curve. In this study, the observed effective clearance rate of the bi-exponential fit function was faster than physical decay (Fig. 1), indicating ongoing biological clearance. By applying physical decay following the last measurement imaging time point in the trapezoidal method, we implicitly assume that biological clearance after the last measurement has not occurred. Consequently, this approach overestimates the actual clearance, leading to an overestimation of the rTIACs. To mitigate this, the monoexponential phase could be integrated using the effective half-life of the radiopharmaceutical rather than the physical half-life alone. While this approach is expected to reduce bias, a more comprehensive evaluation of the trapezoidal-monoexponential method is required to optimize its accuracy.

This study is related to the study by Devasia et al. (2021) [16]. Specifically, we utilized the same dataset and bi-exponential fit function, Eq. (2), within the NLME modeling framework to describe the kinetics of [^{177}Lu]Lu-DOTA-TATE in the kidneys. It is important to note that while Devasia et al. (2021) [16] applied this NLME modeling primarily to investigate the feasibility of reducing imaging time points, the present study aims to evaluate the accuracy of TIAC estimation methods derived from the trapezoidal method relative to the reference from the bi-exponential fit function with NLME modeling. Furthermore, while we adopted the bi-exponential model as the reference here, the fundamental finding regarding the trapezoidal method, specifically its tendency to underestimate or overestimate depending on the tail handling, remains valid regardless of the specific fit function chosen, as these biases are inherent to the trapezoidal integration method itself.

A clear boundary exists between the present study and the referenced work [16]. While Devasia et al. (2021) [16] investigated the accuracy of TIAC estimation using reduced imaging time points, the current study evaluates the methodological aspects of TIAC estimation. We specifically assess the accuracy of the trapezoidal integration method by comparing it against reference values derived from NLME modeling. To the best of our knowledge, this is the first study to systematically quantify the systematic differences between the trapezoidal method and NLME modeling in the context of [^{177}Lu]Lu-DOTA-TATE renal dosimetry. However, the limitation of this study is the relatively small sample size. While the current dataset is sufficient to demonstrate mathematical trends, future studies utilizing larger, multi-center datasets are recommended to further validate these findings across a broader patient population.

Although the exact mathematical representation of radiopharmaceutical kinetics within the human body remains unknown, approximations using sum-of-exponential functions [5] or simplified compartmental models [6,22,30] are valuable, as they account for both empirical observations and the fundamental principles of radiopharmaceutical transfer. In this study, a bi-exponential function, Eq. (2), was utilized under the assumption that it adequately describes the biokinetic data of [^{177}Lu]Lu-DOTATATE in the kidneys [16]. For future applications, a population-based model selection method's [17,31,32], could be employed to objectively identify the fit function most supported by the dataset, which may enhance the robustness of the reference function.

CONCLUSION

In this study on [^{177}Lu]Lu-DOTATATE renal biokinetic data, we demonstrated that TIACs derived from the full trapezoidal method consistently underestimate the reference values, whereas the trapezoidal method combined with a monoexponential physical decay following the last imaging time point results in overestimation. These findings indicate that relying exclusively on trapezoidal integration introduces systematic bias in [^{177}Lu]Lu-DOTA-TATE renal dosimetry. Consequently, while model-based approaches appear advantageous, further comprehensive evaluation using larger patient cohorts is required to fully validate these findings and optimize the curve-fitting strategy for clinical practice.

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AUTHOR CONTR IBUTION

Indra Budiansah performed research, analyzed results, wrote, and checked the manuscript. Deni Hardiansyah designed the retrospective analysis, analyzed results, wrote, and checked the manuscript.

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