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THE EFFECTS OF INTRA-INDIVIDUAL VARIABILITY SETTING ON THE ACCURACY OF TIME-INTEGRATED ACTIVITY CALCULATIONS USING NONLINEAR MIXED-EFFECTS MODELING

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Abstrak

Estimasi yang akurat terhadap *time-integrated activity* (TIA) penting untuk perencanaan pengobatan pada *peptide receptor radionuclide therapy* (PRRT). Dalam konteks pemodelan farmakokinetik, *intra-individual variability* (IAV) — yang berkaitan dengan ketidakpastian pengukuran — dapat memengaruhi estimasi nilai TIA. Penelitian ini bertujuan untuk meneliti dampak variasi pengaturan IAV terhadap perhitungan TIA. Data biokinetik ginjal (PMID: 33443063) dari 10 pasien tumor neuroendokrin setelah pemberian [^{177}Lu]Lu-DOTATATE dianalisis menggunakan SPECT/CT. Estimasi TIA dilakukan menggunakan *Nonlinear Mixed-Effects Modeling* (NLMEM) dengan *error model* proporsional. Metode 1: TIA referensi (rTIA) dihitung dengan mengestimasi *inter-individual variability* (IIV) and IAV. Metode 2: Nilai IAV kemudian ditetapkan menjadi setengah (hTIA) dan dua kali lipat (tTIA) dari nilai yang diperoleh pada Metode 1. Pengaruh perubahan IAV terhadap akurasi TIA dievaluasi dengan membandingkan hTIA dan tTIA terhadap rTIA menggunakan *relative deviation* (RD), *root-mean-square error* (RMSE), dan *mean absolute percentage error* (MAPE). Hasil menunjukkan bahwa penetapan IAV menjadi setengah dari nilai referensi menghasilkan RMSE sebesar 5% dan MAPE sebesar 3%. Sementara itu, perubahan dua kali nilai IAV menghasilkan RMSE sebesar 7% dan MAPE sebesar 6%. Secara keseluruhan, perubahan pengaturan IAV memberikan dampak yang sangat kecil, karena perhitungan TIA tetap stabil dan tidak sensitif terhadap variasi IAV, baik ketika nilainya dikurangi setengah maupun digandakan dalam data biokinetik populasi ini.

Keywords: PRRT, NLMEM, Intra-individual variability (IAV)

Abstract

Accurate estimation of kidney time-integrated activity (TIA) is essential for treatment planning in peptide receptor radionuclide therapy (PRRT). In the context of pharmacokinetic modeling, the intra-individual variability (IAV) setting—associated with measurement uncertainty—may influence TIA estimates. This study investigates the impact of varying IAV settings on TIA calculation. Kidney biokinetic data (PMID: 33443063) from 10 neuroendocrine tumor patients after [^{177}Lu]Lu-DOTATATE administration were analyzed using SPECT/CT. A Nonlinear Mixed-Effects Modeling (NLMEM) with proportional error model was used for TIA estimation. Method 1: reference TIA (rTIA) was calculated by estimating both inter-individual variability (IIV) and IAV. Method 2: IAV was fixed at half (hTIA) and twice (tTIA) the value obtained in Method 1. The influence of altered IAV on TIA accuracy was evaluated by comparing hTIA and tTIA against rTIA using relative deviation (RD), root-mean-square error (RMSE), and mean absolute percentage error (MAPE). Fixing IAV at half the reference value resulted in RMSE and MAPE of 5% and 3%, respectively. Furthermore, doubling the IAV led to an RMSE of 7% and MAPE of 6%. Modifying the IAV setting had a negligible impact as TIA calculation remained robust and insensitive to IAV variations when doubled and halved in our population biokinetic data.

Keywords: PRRT, NLMEM, Intra-individual variability (IAV)

INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTATATE has become a standard treatment for advanced neuroendocrine tumors (NETs), demonstrating significant improvements in progression-free survival and symptom control [1]. Patient-specific calculation of time-integrated activity (TIA) for radiopharmaceuticals in kidney as organs at risk (OAR) is desirable in molecular radiotherapy [2], [3], [4], [5], as it enables personalized dosimetry, minimizes toxicity, and optimizes therapeutic efficacy. The TIA represents the total accumulated activity in tissues over time that is required for determining absorbed dose [6].

Recent studies have highlighted the critical role of pharmacokinetic modeling in TIA calculation, particularly through Nonlinear Mixed-Effects Modeling (NLMEM) approaches that account for interindividual variability (IIV) and intra-individual variability (IAV) [7], [8], [9], [10]. The findings suggest that data type (sparse or rich data) may influence the estimation of IAV, while IIV is less affected in pharmaceutical drug research [11]. In the context of pharmacokinetic modeling, the IAV setting—associated with measurement uncertainty—may influence TIA estimates. Therefore, this study investigates how variations in IAV settings influence kidney TIA estimates in patients receiving [^{177}Lu]Lu-DOTATATE. By elucidating the impact of IAV on the accuracy of TIA calculation, the findings could be used for clinical dosimetry practices.

MATERIALS AND METHODS

Biokinetic Data

This study utilized secondary data of Devasia et al. (PMID: 33443063) [9] from a retrospective clinical analysis of 10 patients who underwent multi-time-point SPECT/CT imaging following one cycle of standard [^{177}Lu]Lu-DOTATATE PRRT for NETs at the University of Michigan Medical Center (August 2018–March 2020). Sequential SPECT/CT imaging (up to 4 time points per patient) was performed on a Siemens Intevo Bold system, with the first scan acquired pre-discharge on the treatment day and subsequent scans at 1–7 days post-therapy, including a targeted ~96-hour time point based on prior dosimetry optimization studies. SPECT reconstruction used Siemens xSPECT Quant software with voxel values in Bq/mL [8], [9], [12]. Kidneys were manually segmented on baseline CT by an experienced technologist, and VOIs were propagated to later time points via contour intensity–based alignment for time–activity data extraction. The pharmacokinetic data of the right kidney and left kidney of 10 patients were treated as distinct, the total dataset comprised 20 pharmacokinetic measurements.

Standard Biexponential Time–Activity Fit for Clinical Patients

The biexponential models (Equation 1) that was used in the original paper analyzing the biokinetic data [9] in describing uptake and clearance of the radiopharmaceuticals, the model was described as follows:

$$A(t_{ij}) = \frac{ke*ka}{c(ka-ke)} \times \left[\exp\left(-ke*t_{ij}\right) - \exp\left(-ka*t_{ij}\right)\right] + \varepsilon(t_{ij}) \tag{1}$$

$$TIA = \int_0^\infty A(t)\,dt = \frac{1}{c} \tag{2}$$

$$i = 1, \ldots, \; n = kidney\ index$$

$$j = 1, \ldots, \; n_i = time\ index$$

Parameter c scales the curve up or down, while ka (uptake/absorption rate) and ke (elimination rate) govern its shape. The term ϵ represents measurement error, assumed measurement error with variance of σ^2_{err} .

Nonlinear mixed effects modelling (NLMEM)

NLMEM provides a framework for assessing both IIV and IAV [13], [14], [15], [16]. The NLMEM parameterizes fixed and random effects. Fixed effects describe the mean values of the estimated parameters in the population, while random effects describe the IIV of the estimated parameters between subjects in the population [17].

$$P_j = TVP_j \times \exp\left(ETA_j\right) \tag{3}$$

$$ETA_j = N(0, \sigma_j^2) \tag{4}$$

Where P_j is the estimated parameter j in a function, TVP_j is the fixed effect of the estimated parameter j, and ETA_j is the random effect. ETA_j is a random number following a Gaussian distribution with mean zero and variance σ_j^2. The proportional error model was used for the NLMEM model fitting [18] account for IAV in the observed kidney time–activity data. NLMEM model fittings and simulations were performed using NONMEM software (version 7.6.0; ICON Development Solutions, Ellicott City, MD).

Variation of IAV parameter settings in TIA calculation

Figure 1 shows the workflow of this study. Kidney biokinetic data from 10 NET after [^{177}Lu]Lu-DOTATATE administration were fitted both IIV and IAV. In method 1, the TIA derived from fitting by estimating both IIV and IAV as the reference TIA (rTIA). Furthermore, in Method 2, the IAV value is varied by fixed at half (hTIA) and and twice (tTIA) the value obtained in Method 1.

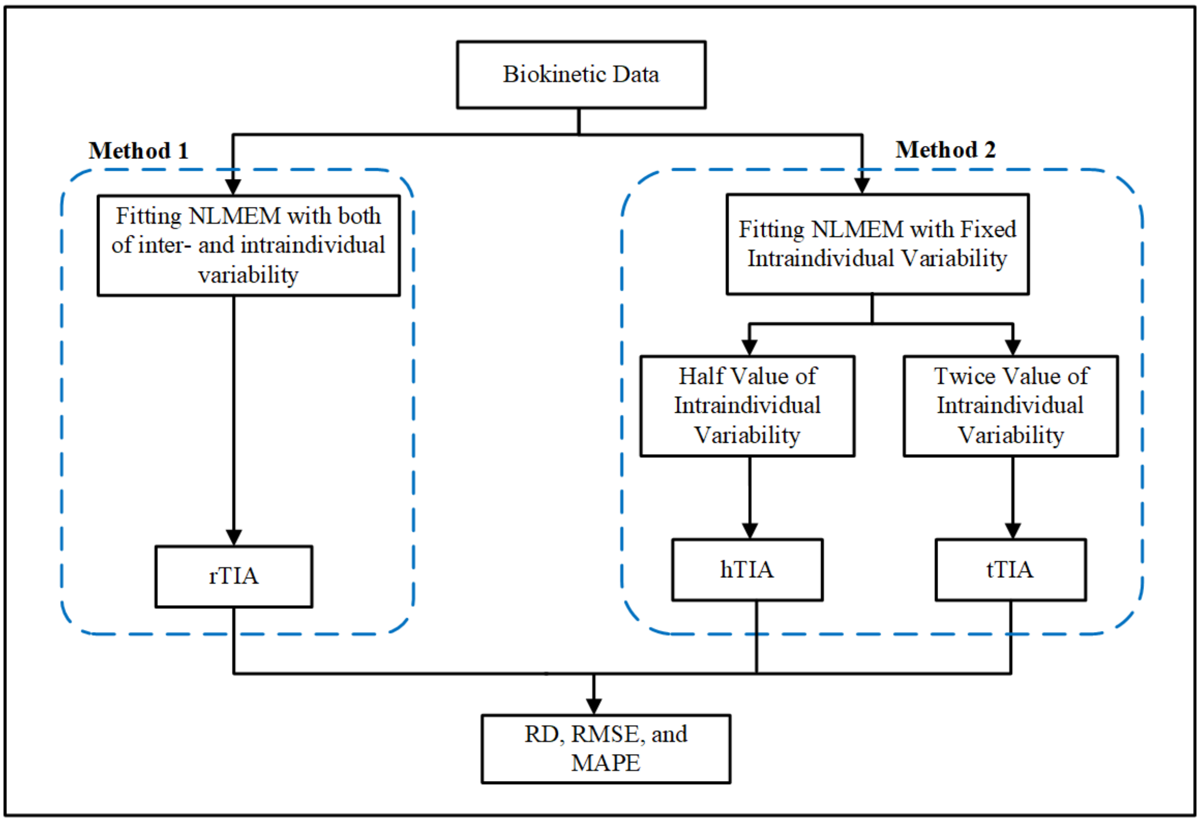

FIGURE 1. Workflow of this study

The influence of altered IAV on TIA accuracy was evaluated by comparing hTIA and tTIA against rTIA using relative deviation (RD), root-mean-square error (RMSE), and mean absolute percentage error (MAPE). The relative deviation RD and the RMSE were calculated according to:

$$RD_k = \frac{kTIA - rTIA}{rTIA} \tag{5}$$

$$RMSE_k = \sqrt{\left(SDRD_k\right)^2 + \left(Mean\ RD_k\right)^2} \tag{6}$$

where $kTIA$ is TIA from each method (k represents a method where h=half original IAV ($hTIA$) or t=twice original IAV ($tTIA$)), $rTIA$ is reference TIA, RD_k is the RD of the each method at k, $RMSE_k$ is the root-mean square of RD_k over all patients, and $SDRD_k$ is the SD of RD_k.

Mean Absolute Percentage Error (MAPE) represents the average of the absolute percentage differences between the TIA estimated from hTIA and tTIA with the rTIA obtained from fitted both IIV and IAV as the reference:

$$MAPE = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{kTIA - rTIA}{rTIA}\right| \times 100\% \tag{7}$$

RESULT AND DISCUSSION

In method 1, the NLMEM fitting incorporating both IIV and IAV yielded an initial estimate of the IAV parameter at 17%, along with the corresponding fitting curve (**Figure 2**) and the estimation result of the IIV obtained a relative standard error (RSE) of less than 50%. In the fitting process, the k_a parameter remained fixed as it was not estimated. Devasia et al. [9] previously demonstrated that all parameters in their bi-exponential model incorporated random effects indicating IIV across each parameter. However, the current study observed no random effects for the parameter k_a, as its variability was negligible (variance < 10^{-6}).

These differences may stem from differences in computational tools and estimation methodologies. Specifically, the present analysis utilized NONMEM version 7.6.0, which implements stochastic approximation expectation maximization (SAEM) coupled with importance sampling (IMP) for objective function computation [19], whereas the prior study employed the Statistical Analysis System (SAS), typically reliant on generalized NLMEM techniques. Discrepancies in estimation algorithms, convergence thresholds, and optimization strategies between software platforms may contribute to minor variations in parameter estimates, as also reported in the literature [20].

For the value of IAV serves as a crucial baseline for evaluating how deviations in fixed IAV can influence model performance. The half and twice multiples of the estimated IAV were 8.5% and 34%, respectively. These values were subsequently used as fixed parameters in method 2.

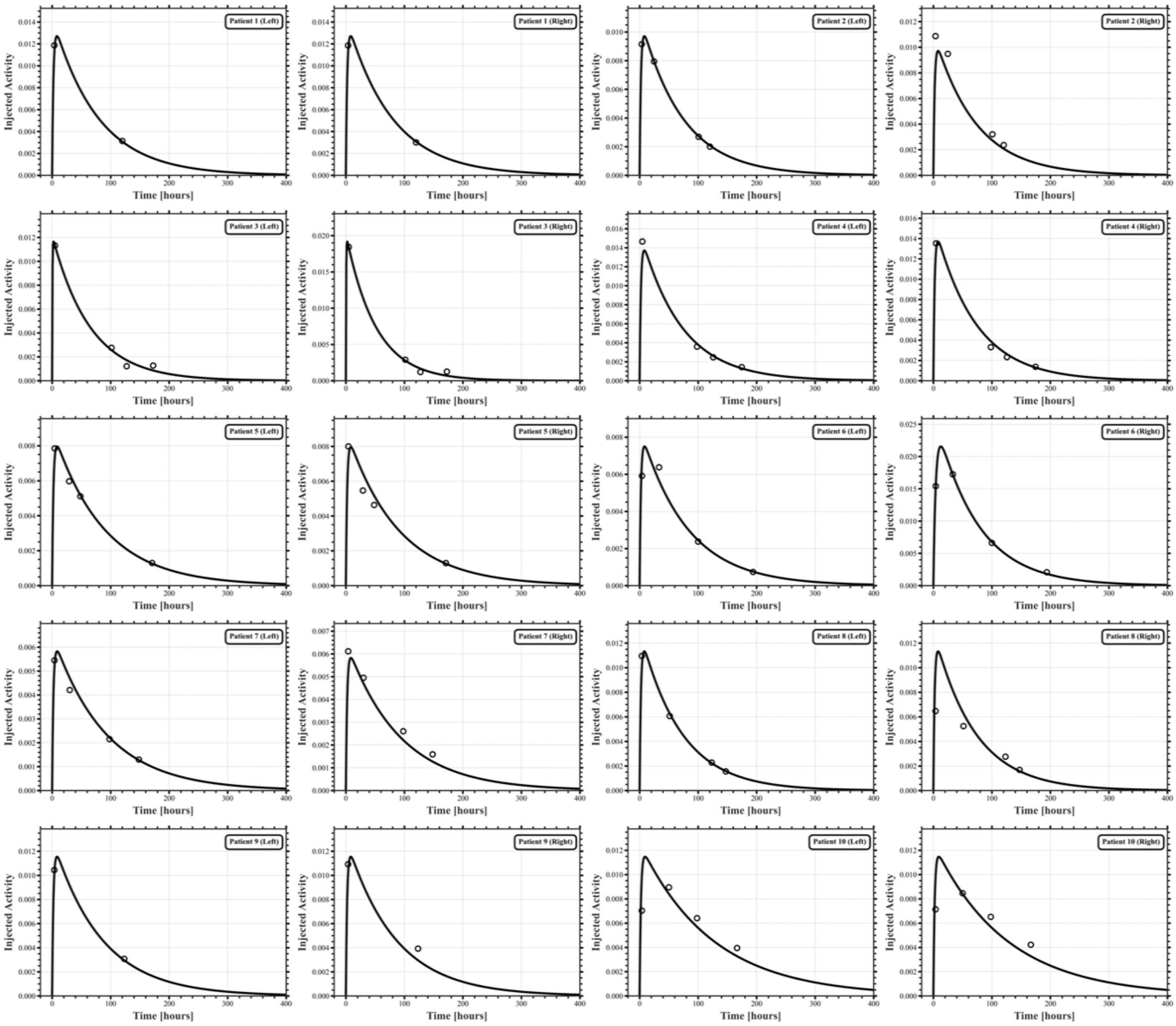

FIGURE 2. Time activity curves of the relationship between injected activity and time from Equation 1 by estimating the IAV value (reference).

For method 2, the fitting results for half and twice the IAV were evaluated to assess their influence on TIA estimation, based on the analysis of RD, RMSE, and MAPE (**Figure 3** and **Table 1**). The

RMSE and MAPE values obtained with half the IAV were 4.92% and 3.10%, respectively, while the RMSE and MAPE values with twice the IAV were 6.80% and 5.52%.

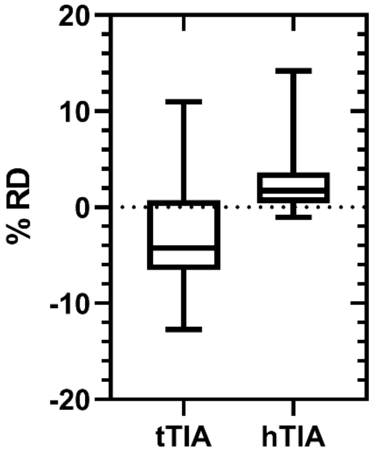

FIGURE 3. RD of TIA obtained using fixation IAV

TABEL 1. RD value of TIA obtained using fixation IAV

Intra-individual variability (IAV) Fixed	RD%		RMSE of the RD(%)	MAPE(%)
	Mean (SD)	Median [Min, Max]		
8.5%	2.94 (3.95)	1.76 [-1.06,14.19]	4.92	8.5%
34%	-3.22 (5.93)	-4.25 [-12.72,10.99]	6.80	34%

As shown in **Figure 3** and **Table 1**, the TIA obtained with twice the fixed IAV showed marginally higher deviations compared to the reference, while deviations with half the IAV remained minimal. However, despite the slightly elevated errors with doubled IAV, both scenarios maintained sufficiently low RD, RMSE, and MAPE values to be considered negligible in practice. This confirms that fixing the IAV value—whether halved or doubled—has minimal impact on TIA accuracy, suggesting that the TIA calculation is robust and insensitive to variations in predefined IAV values. Thus, while careful assessment of IAV levels is advisable, the method remains reliable even when fixed values are applied.

This study has several limitations. First, the analysis relied on a single dataset, and second, only a narrow range of fixed IAV values (8.5% and 34%) was examined. These constraints may limit the ability to capture the full variability observed in broader clinical settings. Consequently, the generalizability of the findings remains uncertain. Future studies should validate these results using larger, more diverse datasets and a wider range of fixed IAV values.

CONCLUSION

This study demonstrates that fixed IAV values whether halved (RMSE: 4.92%, MAPE: 3.10%) or doubled (RMSE: 6.80%, MAPE: 5.52%) yield clinically acceptable TIA accuracy. TIA calculation remains robust and insensitive to IAV variations, even when the parameter is fixed at predefined values in our population biokinetic data.

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