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EFFECT OF PATIENT'S GENDER ON THE CALCULATION OF TIME-INTEGRATED ACTIVITY COEFFICIENT IN RADIONUCLIDE THERAPY: STUDY WITH NON-LINEAR MIXED-EFFECTS MODEL

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Abstrak

Tujuan: Penelitian ini bertujuan untuk meninjau pengaruh dari jenis kelamin pasien terhadap perhitungan *time-integrated activity coefficient* (TIAC) pada terapi radionuklida. Metode: Penelitian ini menggunakan data biokinetik ginjal (PMID: 33443063) dari 10 pasien (6 laki-laki, 4 perempuan) yang diberikan penanganan [^{177}Lu]Lu-DOTATATE. Fungsi bi-eksponensial digunakan untuk memodelkan fase penyerapan (*uptake*) dan peluruhan (*clearance*). TIAC referensi (rTIAC) ditentukan dengan melakukan *fitting* pada parameter fungsi bi-ekxponensial pada semua data dengan permodelan *non-linear mixed-effects model* (NLMEM). Untuk meninjau pengaruh jenis kelamin, *fitting* NLMEM berbeda dilakukan pada sub-kelompok laki-laki dan perempuan sehingga dihasilkan TIAC estimasi (eTIAC). rTIAC dan eTIAC dibandingkan dengan menghitung deviasi relatif (RD) dan *root-mean square error* (RMSE). Jenis kelamin dianggap berpengaruh apabila RD dan RMSE melebihi 27%. Hasil: Nilai RD untuk sub kelompok laki-laki adalah -4.1% ± 7.2% dengan RMSE 8.3%. Nilai RD untuk sub kelompok perempuan adalah 5.2% ± 7.8% dengan RMSE 9.4%. Kesimpulan: Untuk terapi [^{177}Lu]Lu-DOTATATE pada data biokinetik yang diuji pada studi ini, jenis kelamin tidak menunjukkan pengaruh pada perhitungan TIAC.

Kata-kata kunci: TIAC, Jenis Kelamin, Terapi Radionuklida.

Abstract

Purpose: This study investigates the influence of patient gender on the calculation of the Time-Integrated Activity Coefficient (TIAC) in radionuclide therapy. Methods: Kidney biokinetic data (PMID: 33443063) from 10 patients (6 males, 4 females) treated with [^{177}Lu]Lu-DOTATATE were analysed. A bi-exponential function was used to model both the uptake and clearance phases. The reference TIAC (rTIAC) was determined by fitting bi-exponential parameters to the complete dataset using a Non-Linear Mixed-Effects Model (NLMEM). To assess gender impact, separate NLMEM fittings for male and female subgroups yielded estimated TIACs (eTIACs). rTIAC and eTIAC values were compared using Relative Deviation (RD) and Root-Mean-Square Error (RMSE). Gender was deemed impactful if RD or RMSE exceeded 27%. Results: For males, the RD value was -4.1% ± 7.2% and the RMSE value was 8.3%. For females, the RD value was 5.2% ± 7.8% and the RMSE value was 9.4%. Conclusions: For [^{177}Lu]Lu-DOTATATE therapy in this study's tested biokinetic data, gender does not appear to be a major determinant in TIAC calculation, as deviations remain within an acceptable range for most patients..

Keywords: TIAC, Gender, Radionuclide Therapy.

INTRODUCTION

Cancer is a disease with significant global impact. In 2022, nearly 20 million new cancer cases were reported, with almost 10 million (9.7 million) resulting in mortality [1]. One approach to cancer treatment is radionuclide therapy, which utilises administration of radiopharmaceutical [2]. The radiopharmaceutical facilitates targeted delivery of the radionuclide to specific organs, enabling its function either for diagnostic imaging or therapeutic intervention.

Two widely applied radionuclide therapies include peptide receptor radionuclide therapy (PRRT) and [^{177}Lu]Lu-PSMA therapy. PRRT is commonly used for the treatment of neuroendocrine tumours (NETs) [2] whereas [^{177}Lu]Lu-PSMA therapy is employed for prostate cancer [3]. A retrospective analysis of 2022 cancer data indicates that neuroendocrine tumours exhibited the highest mortality rate among tumour types [1]. This highlights the importance of PRRT as a subject of further investigation and analysis.

One of the key challenges in radionuclide therapy is the calculation of the radiation absorbed dose. The absorbed dose in radionuclide therapy is estimated by considering two factors: the Time-Integrated Activity Coefficient (TIAC) and the S value [4]. TIAC represents the accumulated activity over time, derived from the area under the patient's time-activity curve [5]. In contrast, the S value is influenced by organ geometry, organ mass, and the type of radionuclide used. Inter-patient variability in the S value has a minimal impact on dose calculation [6], making TIAC a critical parameter in radionuclide therapy dosimetry.

TIAC calculation can be improved by examining factors influencing its estimation, known as covariates. These factors arise from patient-specific attributes (such as body weight, height, and other physiological parameters) or population-level characteristics (such as ethnicity and genetic background) [7], [8]. Identifying and incorporating relevant covariates can enhance the precision of TIAC calculations while reducing the imaging burden.

In nuclear medicine, the influence of covariates has been explored in various imaging contexts, including ^{131}I uptake in benign thyroid conditions [9], Sacroiliac Joint Scintigraphy [10], and ^{99m}Tc myocardial imaging [11]. These studies have demonstrated that gender can play an important role in radiopharmaceutical kinetics. Understanding such effects may have clinical implications in settings where sex-specific physiology is relevant, such as maternity or paediatric hospitals, which may employ nuclear medicine procedures.

However, previous investigations have predominantly focused on imaging parameters, with limited evaluation of gender's impact on fitting process of therapeutic dose estimation. Specifically, the effect of gender on absorbed dose calculations in the context of PRRT. This study seeks to address this gap by assessing the role of gender in PRRT dosimetry through comparative analysis of TIAC calculated using population data with combined gender and calculated separately between gender.

MATERIALS AND METHOD

Biokinetic Data

Biokinetic data from the right and left kidneys of 10 patients administered [^{177}Lu]Lu-DOTATATE were analysed (PMID: 33443063). Among these patients, six were male and four were female. The left and right kidneys were treated as distinct subjects and included separately in the population analysis. All participants underwent multiple-time-point SPECT/CT imaging following one cycle of standard [^{177}Lu]Lu-DOTATATE PRRT for NETs, conducted at the University of Michigan Medical Center between August 2018 and March 2020 [12]. The study received Institutional Review Board approval, and all patients provided written informed consent.

SPECT imaging parameters: Medium-energy collimator, 1.5 cm crystal, 256 × 256 matrix, 60 views per head, 30 seconds per view, 20% main window at 208 keV, and adjacent 10% scatter windows. SPECT reconstruction was performed using Siemens xSPECT Quant, employing 48 iterations, 1 subset, resolution recovery, attenuation correction, and triple-energy-window scatter correction in a 256 × 256 matrix with 2 mm³ voxel size. No post-reconstruction smoothing was applied. CT imaging

parameters: Acquired with free breathing in low-dose mode, using 120 kVp, 80 mAs at the first time point, and 15 mAs at subsequent time points. The CT matrix size was 512 × 512 × 130, with a voxel size of 0.97 × 0.97 × 3 mm³.

Non-Linear Mixed-Effects Model

A biexponential model [13] describing uptake and clearance of the radiopharmaceuticals was used, the model was described as follows

$$A(t) = \frac{k_e * k_a}{c(k_a - k_e)}[\exp(-k_e t) - \exp(-k_a t)] \quad (1)$$

where k_a, k_e, c were the parameters of uptake rate, decay rate, and a constant, respectively. Each parameter was optimised through fitting method. The value of TIAC from the equation were evaluated analytically with

$$TIAC = \frac{1}{c} \quad (2)$$

The fitting was performed within the Non-Linear Mixed-Effects Modelling (NLMEM) framework [14], [15], [16]. The residual error was set to be proportional to the model function with estimated percentage of error (fractional standard deviation), this will represent the intra-individual variability. Furthermore, each parameter is modelled as follows

$$p = \exp(TV_p + \eta_{p,i}) \quad (3)$$

where TV_p is the fixed effect or the typical value of parameter p which have the same value for all patients, $\eta_{p,i}$ is the random effect or inter-individual variability of parameter p for patient i which differentiate the value of parameter between patients. The value of $\eta_{p,i}$ are distributed normally with mean 0 and variance ω_p^2 [17], [18].

Study Workflow

The study was initially conducted by fitting all patient data within the NLMEM framework. The resulting TIAC for each patient were designated as reference TIACs (rTIACs). To evaluate the impact of gender, separate NLMEM fittings were performed for male and female subgroups, producing estimated TIACs (eTIACs). Comparisons between rTIACs and eTIACs were made using Relative Deviation (RD) and Root-Mean-Square Error (RMSE). RD and RMSE metrics were computed to quantify discrepancies and assess model performance across gender groups. The RD and RMSE were calculated as follows

$$RD_i(\%) = \frac{eTIAC_i - rTIAC_i}{rTIAC_i} \times 100\% \quad (4)$$

$$RMSE = \sqrt{(meanRD)^2 + (SDRD)^2} \quad (5)$$

where eTIAC_i and rTIAC_i were estimated and reference TIAC for patient i respectively, meanRD and SDRD were mean and standard deviation of the RD for each subgroup. Gender was deemed impactful if RD or RMSE exceeded 27% [19]. The workflow of this study can be seen in **Figure 1**.

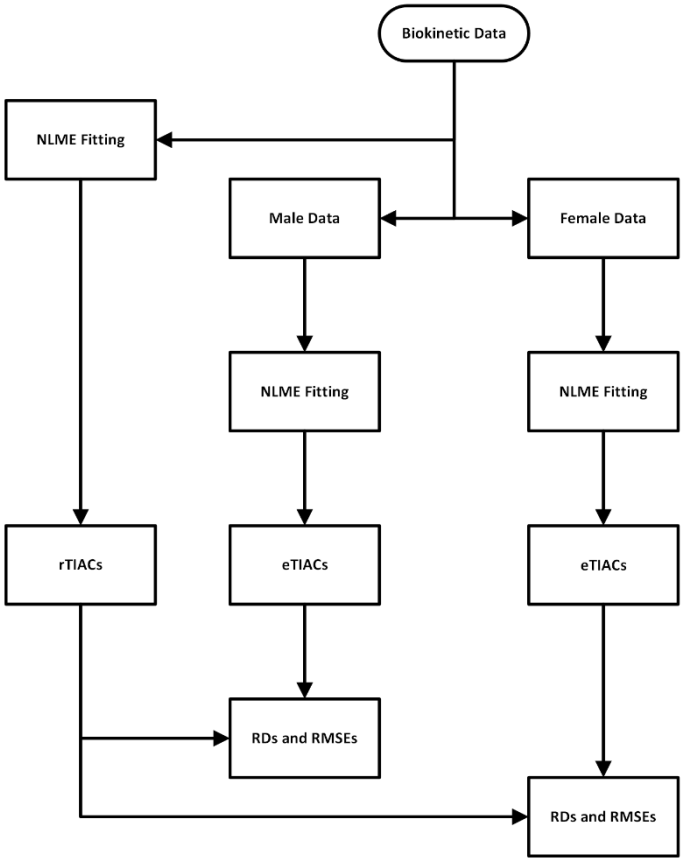

FIGURE 1. The workflow of this study. All patients were fitted with NLMEM framework to get the reference TIAC (rTIACs). Each group of male and female were fitted separately with NLMEM framework to get the estimated TIAC (eTIACs). The comparison of rTIACs and eTIACs was evaluated by calculating the RD and RMSE. NLMEM: Non-Linear Mixed-Effects Modelling, TIAC: Time-Integrated Activity Coefficient, RD: Relative Deviation, RMSE: Root-Mean-Squre Error.

RESULTS

The RD values for TIACs between reference and gender-specific estimations are summarised in **Table 1**. The data comprise separate evaluations for the left and right kidneys of male and female patients administered [^{177}Lu]Lu-DOTATATE. Values exceeding ±10% RD are highlighted in bold and indicate cases where gender-specific fitting may result in notable discrepancies from population-based reference TIACs.

For male patients, RD values ranged from −14.9% to 7.9%. The highest positive RD was observed in the left kidney of Patient 2 (7.9%), while the largest negative RD occurred in the right kidney of Patient 9 (−14.9%). In the female subgroup, RD values varied from −2.2% to 18.1%, with the most pronounced positive RD found in the right kidney of Patient 10 (18.1%), and the largest negative RD in the left kidney of Patient 7 (−2.2%).

Overall, the mean RD values for male subjects was (-4.1% ± 7.2%) with the RMSE value of 8.3%. For female subjects, the mean RD was (5.2% ± 7.8%) with the RMSE value of 9.4%. These findings suggest that while most deviations remain within an acceptable range, individual cases can exhibit considerable variation.

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TABLE 1. RD values for male and female TIACs based on gender-specific NLMEM fitting.

Male			Female		
Patient	**Position**	**RD (%)**	**Patient**	**Position**	**RD (%)**
1	Left Kidney	-10.6	5	Left Kidney	-0.3
	Right Kidney	-9.6		Right Kidney	-1.0
2	Left Kidney	7.9	6	Left Kidney	2.8
	Right Kidney	0.2		Right Kidney	10.2
3	Left Kidney	2.7	7	Left Kidney	-2.2
	Right Kidney	-8.9		Right Kidney	0.1
4	Left Kidney	-7.6	10	Left Kidney	14.1
	Right Kidney	-5.2		Right Kidney	18.1
8	Left Kidney	0.1			
	Right Kidney	5.7			
9	Left Kidney	-8.9			
	Right Kidney	-14.9			

DISCUSSION

This study investigated the influence of gender on TIACs for [^{177}Lu]Lu-DOTATATE therapy using biokinetic data from multiple-time-point SPECT/CT imaging. Results indicated that most RDs between gender-specific TIAC estimations and rTIACs remained below 27%, suggesting limited impact of gender to the fitting process in the tested dataset.

While certain patients exhibited notable deviations (e.g., RD >10% in two male and three female kidneys), these instances were not consistently observed across the patient and may reflect inter-individual variability rather than systemic gender-based trends. The reduction in sample size following gender stratification may have further contributed to the observed deviations. Moreover, even though some individual has RDs higher than 10%, this value is still in the threshold value of 27%.

Overall, the findings indicate that gender does not influence dosimetry outcomes for [^{177}Lu]Lu-DOTATATE therapy. Comparable results were obtained whether TIACs were calculated using a combined-gender population data or separate gender-specific population data. While previous studies have identified gender as a meaningful factor in certain nuclear medicine procedures [9], [10], [11], such effects are likely to be modality- or tracer-dependent. The lack of a consistent gender-related influence in this study suggests that incorporating gender alone is unlikely to enhance model performance or improve individualised dosimetry in [^{177}Lu]Lu-DOTATATE-based PRRT.

Nevertheless, the observed patient-level deviations highlight the importance of further exploration of additional covariates to explain the inter-individual variability to refine personalised dosimetry. Recently, covariate analysis gained attention for studies [6], [7], [19], [20], [21], but it is limited to the field of pharmacy. It is possible to perform similar studies in the field of nuclear medicine to optimise dosimetry of radionuclide therapy (e.g. reduction of time point [12]). Future studies with larger patient datasets and additional physiological, anatomical, or molecular covariates may also offer improved

stratification and contribute to more robust modelling for clinical implementation of radionuclide therapy.

CONCLUSION

This study investigated the influence of gender on TIAC estimation in [^{177}Lu]Lu-DOTATATE therapy using NLMEM. The findings suggest that, in the tested patient dataset, gender does not affect TIAC estimation, especially to the fitting methods (combined vs separate gender fitting), with most RDs remaining within acceptable limits.

These findings indicate that while fitting with gender-specific separately may offer marginal effect in select cases, it is unlikely to improve overall dosimetry accuracy in PRRT. Future work should explore larger populations and incorporate additional covariates—such as age, glomerulus filtration rate, etc.—not only to the fitting methods but also to explain inter-individual variability to support more robust and personalised dosimetry approaches in radionuclide therapy.

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