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The Accuracy of TIAC Calculated Using SPECT/CT Imaging Data at 36- and 100-Hours Post Injection and Prior Information in ^{177}Lu-DOTATATE

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ABSTRACT

In internal radionuclide therapy, there is a growing demand for streamlined methods that alleviate the measurement burden on patients and reduce the associated costs of individual dosimetry. This study assessed the precision of the Two Time Point Dosimetry (2TPD) model, a data-efficient approach, compared to the well-established All Time Point Dosimetry (ATPD) model. The investigation involved the analysis of time-activity data collected from the kidneys of seven patients who were administered ^{177}Lu-DOTATATE and underwent SPECT/CT imaging (PMID 3344306). Data points were specifically gathered at the 36-hour and 100-hour post-injection marks. Employing prior information, a monoexponential function was applied to fit the biokinetic data. Consequently, two crucial metrics, TIAC ATPD and TIAC 2TPD, were computed for ATPD and 2TPD, respectively. To provide a benchmark, the TIAC determined via the Hänscheid method was also incorporated for comparison. The comparative analysis revealed that the percentage error between the population ATPD model and the 2TPD model was (3.97 ± 7.85)%, and for the Hänscheid model, it was (1.8 ± 7.9)%. These findings affirm that the accuracy of TIAC values derived from the 2TPD approach, leveraging prior-information fitting, is reasonably satisfactory.

1. INTRODUCTION

Clinical applications of internal radiation therapy, also known as molecular radiotherapy, have been carried out in several hospitals in Indonesia, one of which is Peptide Receptor Radionuclide Therapy (PRRT) (Thundimadathil, 2012). PRRT is mainly performed in treating neuroendocrine tumors (Haug, 2020). PRRT uses radiolabeled somatostatin analogs to target somatostatin receptors. Using this approach, potential individual differences in biodistribution are accounted for (Hardiansyah et al., 2016). In this therapy, beta-emitting radionuclides are labelled with pharmaceuticals such as octreotide for therapeutic purposes (Maaß et al., 2016). The two main parameters in determining the absorbed dose based on the Medical Internal Radiation Dose (MIRD) formulation are the time-integrated activity coefficient (TIAC) and S-value (Bolch et al., 2009).

Determining TIAC with the many imaging, i.e., 4 to 5 imaging called the all-time point data (ATPD), the method is challenging for its application, such as the high cost of treatment (Glatting et al., 2013). Considering the need for medical imaging equipment, this method is also time-consuming. To overcome these obstacles, a more effective way is needed. One method is the Single Time Point Dosimetry (STPD) method (Hänscheid et al., 2018).

Many studies have recently been conducted using STPD, leading to relatively accurate TIAC determinations (Vicini et al., 2008). Miederer et al. (2012) studied the STPD from 24 patients with imaging using an octreotide scan to the amount of activity decay measured over 72 hours for the ^{177}Lu nuclide. The results showed that thorough quantification of a 4-hour scan at a single time point appears sufficient to predict the expected renal dose for radionuclide therapy. Other research has also considered the error distribution of TIAC with the STPD method for individual patient dosimetry in radionuclide therapy. This study used the cumulative distribution function and probability density function for analysis. The main results of the study obtained a relatively small error distribution for the estimation of the TIAC values (Gustafsson & Taprogge, 2022). Hou et al. (2021) has also analyzed the STPD method at two different time points and evaluated the dose uncertainty for several radiopharmaceuticals based on the effective half-life distribution. The study showed that lognormal distribution is more appropriate to predict the effective half-life distribution in neuroendocrine tumors, including kidney organs. Hänscheid et al. (2018) conducted radiation-absorbed dose mapping with ^{177}Lu-DOTATATE/-TOC injection using the STPD model. The mapping was carried out with dose calculations using empirical equations, and it was found that the STPD model could lead to a relatively good accuracy.

From some of the above studies, it can be seen that internal radiation therapy using the STPD method is feasible. However, it still has its shortcomings, e.g., Devasia has combined the two-time point data (2TPD) at 100 hours and 4 hours after injection and compared it with STPD, then obtained a relatively better result of TIAC value accuracy in a few patients. However, no one has combined the 2TPD model at 100 hours and 36 hours after injection. Thus, this study aimed to investigate and compare the accuracy of TIAC calculations obtained from the ATPD model to the 2TPD model at 100 and 36 hours after injection. The biokinetic data of the kidneys in seven PRRT patients injected with the radiopharmaceutical ^{177}Lu-DOTATATE was used. We compared the TIAC values obtained from calculating four data points in ATPD as a reference with TIAC values obtained from two measurement data points 2TPD using a monoexponential function and prior-information fitting method.

2. METHOD

Seven consecutive patients with metastasized neuroendocrine tumors (NET) were scheduled for one PRRT cycle using ^{177}Lu-DOTATOC that were included in the total (Devasia et al., 2021). A mean injected activity of 7267 MBq of ^{177}Lu-DOTATOC was injected, and SPECT/CT was performed at (4 ± 0.4) hour, (36 ± 10.5) hour, (100 ± 1.5) hour, (124 ± 2.9) hour, and (168 ± 16.8) hour post-injection. Of all the measurement times, only 2 data were taken at (36 ± 10.5) hours and (100 ± 1.5) hours to analyze 2TPD. The patient data of 2TPD used in this study were Patient 1 for left and right kidney (P1L and P1R), Patient 5 for left and right kidney (P5L and P5R), and Patient 6 for left and right kidney (P6L and P6R). The SAAM II Numerical software fits the monoexponential function to the ATPD measurement with prior information methods for each patient. Matlab R2020 with license number 40515036 was used to determine the area under the curve. The monoexponential used in this study was:

$$f1(t) = Ae^{-(\lambda 1+\lambda \mathrm{phys})\mathrm{t}} \tag{1}$$

where A is the radioisotope activity value, $\lambda 1$ is the biological decay constant, $\lambda phys$ is the physical decay constant, and t is the decay time (Cherry et al., 2012).

After fitting using a monoexponential function, the Area Under the Curve (AUC) value was calculated. AUC is obtained from the integration of the activity curve against time, shown by the equation below:

$$AUC = \int_0^t A(r_s, t)dt \tag{2}$$

The TIAC value was calculated using parameters A, $\lambda 1$, and $\lambda phys$ from the monoexponential function. Where A is the prefactor, $\lambda 1$ is the biological decay constant, and $\lambda phys$ is the physical decay

constant with a value of 0.0043 hours (Kam et al., 2012). TIAC value was calculated by dividing the AUC value by the injection activity values using the formula below:

$$TIAC = \frac{1}{A_0}\int_0^t A(r_s,t)dt \quad (3)$$

The values of *A*, *λ1*, and *λphys* in each patient from the previous fitting were combined with other patients using a jackknife and then processed using the prior-information fitting method (Glatting et al., 2007). An advanced version of the least square maximum likelihood objective function (OF) was required to estimate the adjustable parameters of the fit functions and the data variance, possibly including knowledge from previous investigations. The product of the likelihood of the observed data (time activity data) and the prior distribution, i.e., a priori knowledge of parameter values that may be available from previous experiments or studies, was derived from the OF,

$$-2\ln(P) = \sum_{i=1}^{N}\left\{\ln(2\pi\theta_i^2) + \ln(v) + \frac{(y_i - f(x_i))^2}{\sigma_i^2}\right\} + \sum_{j=1}^{K}\left\{\ln(2\pi\omega_i^2) + \ln(v) + \frac{(P_j - \overline{P_j})^2}{\omega_j^2}\right\} \quad (4)$$

where *P* is the likelihood, *N* and *K* are the numbers of data points and adjustable parameters, y_i and $f(x_i)$ are the measured data point and function value for the $_i$th sample time, θ_i^2 is the variance, *v* is the scaling factor, and σ_i^2 is the scaled variance. P_J is the current parameter *j*, P_j is the average population value, and ω^2_j is the standard deviation.

The TIAC Hänscheid was calculated using the following equation:

$$\tilde{a}(r_s,t) = \frac{1}{\ln 2} \times A(t) \times 2t \quad (5)$$

where $\tilde{a}(r_s,t)$ is the TIAC value, $A(t)$ is the radioisotope activity value, and t is the measurement time.

After obtaining the TIAC value of ATPD and 2TPD, the absorbed dose value of all existing fitting models can also be calculated. The absorbed dose value can be calculated by summing the TIAC value and *S*-value, which can be seen in Equation 5 (Siegel et al., 1999).

$$D(r_k \leftarrow r_h) = \sum_i \tilde{A}_h S(r_k \leftarrow r_h) \quad (6)$$

Where $D(r_k \leftarrow r_h)$ is the absorbed dose, $\tilde{A}_h$ is TIAC value, and $S(r_k \leftarrow r_h)$ is S-value. This study used the ^{177}Lu-DOTATATE radiopharmaceutical and specialized the kidney organ, so an S-value of 4.82×10^{-6} Gy.min^{-1}.MBq^{-1} was used (Jiménez-Franco et al., 2021).

3. RESULTS AND DISCUSSION

3.1 Fitting Result

The goodness-of-fit test was checked by visual inspection of the plotted curve, the coefficient of variation (CV), and the coefficient of the matrix (CM) values (Kletting et al., 2013). An example of the fitting result of ATPD and 2TPD can be seen in Figure 1.

Figure 1 shows an example of the ATPD model fit results. Figure 1a shows that the relevant data using the monoexponential function was relatively good. Furthermore, using the jackknife method, the data from the fitting development of the ATPD model obtained parameters were then used as prior-information parameters for STPD and 2TPD appropriate models.

The 2TPD data fitting used the same starting values parameters as in ATPD fitting. The difference lies only in the number of time points used. This is done to compare the accuracy of the

fitting results from the STPD model. Figure 2 shows an example of patient one left kidney appropriate results using two-time point measurements. The graph also shows that the monoexponential function can pass through both data points accurately depending on the distribution. Devasia et al. (2021) research also performed fitting with two-time points and obtained reasonably accurate results. Similar to the ATPD model, the Area Under the Curve (AUC) value for the 2TPD model can also be calculated from the graph, which can then be used to calculate the TIAC value.

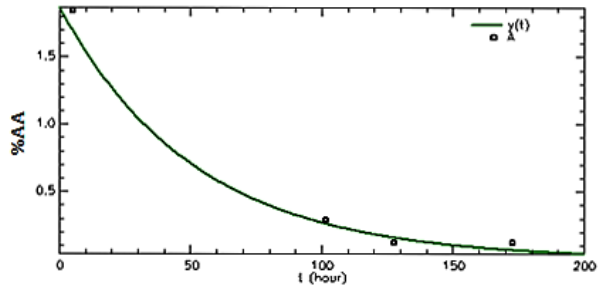

Figure 1 Graph of ATPD fitting results for patient one left kidney

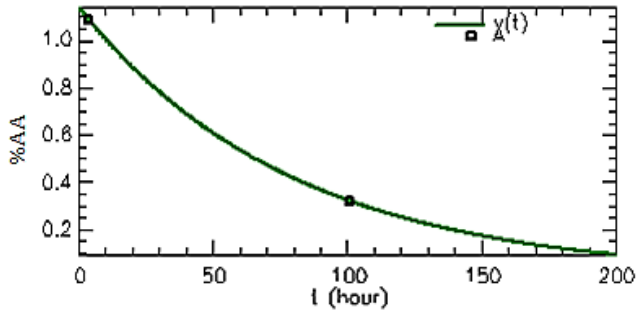

Figure 2 Graph 2TPD fitting results for patient one left kidney

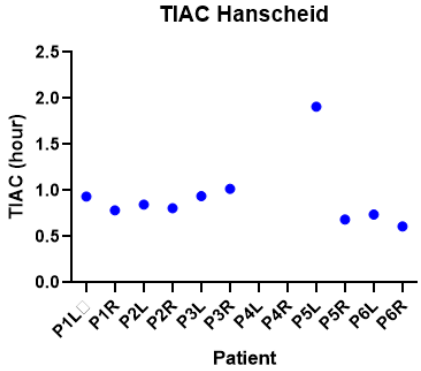

Figure 3 TIAC value of each patient with the Hänscheid method

3.2 TIAC Value of Hänscheid Method

Determining TIAC values with the Hänscheid method does not require data fitting as in the STPD and 2TPD models. Hänscheid has determined the mathematical equation for calculating the TIAC value. The determination of the TIAC value in the Hänscheid method is only done at one measurement time. Therefore, the same measurement time as the STPD model was chosen at (100 ± 1.5) hour post-injection for further comparison. The TIAC value of each patient calculated by the Hänscheid method at time (100 ± 1.5) is shown in Figure 3.

Figure 3 shows a graph of the TIAC value of each patient (P1L-P6R) calculated by the Hänscheid method. The TIAC values for the left and right kidneys for patient 1 were 0.93 hours and

0.78 hours, patient 2 were 0.85 hours and 0.81 hours, patient 3 were 0.94 hours and 1.02 hours, patient 5 were 1.91 hours and 0.69 hours, and patient 6 are 0.74 hours and 0.61 hours. The difference in TIAC values produced by each patient is due to the physiological differences of the patient, Such as the patient's weight, which causes differences in kidney size so that each patient will produce a different flow or uptake of radiation.

3.3 Model Accuracy Level against ATPD

The AUC value of the 2TPD and Hänscheid model was compared with the ATPD model. The model comparison is done by calculating the *%RD* value of each model. The combination of ATPD with 2TPD was named ATPD_G3-2, while with Hänscheid was named ATPD_ Hänscheid.

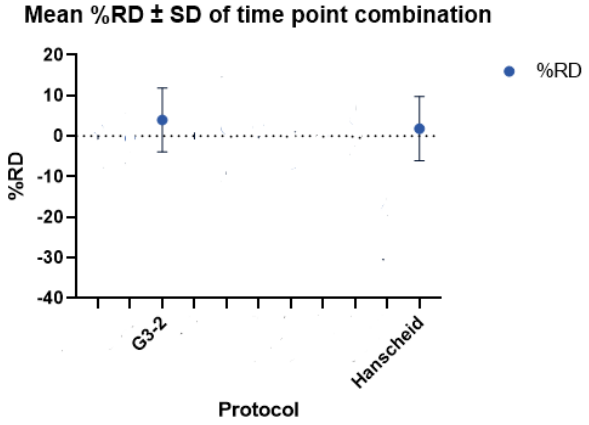

Figure 4 Comparison of *%RD* AUC of 2TPD and Hänscheid model against ATPD model

The mean %RD values produced by the ATPD_ G3-2 time point combination were (3.97 ± 7.85) %, as shown in Figure 4. This means that the AUC value generated by the time point combination of the 2TPD model, i.e., at (36 ± 10.5) hour and (100±1.5) hour p.i., was close to the AUC value generated by the ATPD model. This value was quite good, as seen from the relatively small *%RD*. Figure 4 also shows the mean *%RD* values produced by the ATPD_Hänscheid was (1.8 ± 7.9)%. This means that the AUC value generated by the Hänscheid model was relatively good.

3.4 TIAC Value using the Bayesian Method

The TIAC values of the ATPD model, which is the reference TIAC and TIAC 2TPD model, were calculated by the prior-information fitting method, TIAC Hänscheid obtained from the calculation results using a one-time point which was (100 ± 1.5) hour post-injection. The TIAC values of the ATPD, 2TPD, and Hänscheid models for all patients can be shown in Table 1.

Table 1 TIAC value of each patient (hour)

Patient	TIAC ATPD	TIAC 2TPD	TIAC Hänscheid
1L	0.92	0.98	0.93
1R	0.78	0.82	0.78
5L	1.70	1.99	1.91
5R	0.63	0.74	0.69
6L	0.70	0.74	0.74
6R	0.58	0.61	0.61

Table 1 shows the TIAC values of Patient 1 for the left and right kidneys, patient 5 for the left and right kidneys, and patient 6 for the left and right kidneys. The TIAC values generated from each model have relatively similar values for all right and left kidney patients. Table 1 shows that the 2TP

model is quite accurately used for the calculation of TIAC values; this model also provides advantages in the form of less measurement time compared to the ATPD model.

3.5 Absorbed Dose Value using the Bayesian Method

The absorbed dose of each patient can be determined by calculating the TIAC value obtained in each patient with the S-value (Gear et al., 2018). The S-value is different for each radiopharmaceutical and organ. A comparison of the absorbed dose values of each model in all patients for both the left kidney and right kidney can be seen in Table 2.

The Bayesian method also calculated the absorbed dose value of 2TPD and the Hänscheid model. TIAC Hänscheid was obtained from the calculation results using a one-time point (100±1.5) hour post-injection. The absorbed dose values of the ATPD, 2TPD, and Hänscheid models for all patients can be shown in Table 2.

Table 2 Absorbed Dose value of each patient (Gy/MBq)

Patient	AD ATPD	AD 2TPD	AD Hänscheid
1L	1.89	1.99	2.00
1R	1.60	1.69	1.68
5L	3.62	3.84	4.08
5R	1.33	1.54	1.47
6L	1.52	1.44	1.58
6R	1.26	1.21	1.30

Table 2 shows the absorbed dose values of Patient 1 for the left and right kidneys, patient 5 for the left and right kidneys, and Patient 6 for the left and right kidneys. Table 2 shows that the absorbed dose values generated from each model have relatively similar values for all right and left kidney patients. Meanwhile, the difference was significant in patient 5 for the left kidney. It might happen because the radioactive activity measured in this patient was relatively high compared to the other patients. The Bayesian method shows the accuracy of absorbed dose values for each patient from the data above.

Toxicity treatment-related kidney toxicity has not been reported despite extended follow-up for patients receiving a kidney dose over 28 Gy, indicating that this may be a conservative limit (Bergsma et al., 2016). Also concerning that, the absorbed dose value obtained in this study is safe for patients.

4. CONCLUSION

The 2TPD model exhibits a commendable accuracy when employed to determine TIAC values in internal radiation therapy dosimetry, utilizing the prior-information method. Furthermore, we conducted a rigorous comparative analysis, which included the evaluation of TIAC accuracy using the Hänscheid method as a reference point. Our findings unveiled that the 2TPD model achieved an accuracy rating, as indicated by the *%RD* value, with a mean of 3.97% and a range of ±7.85%. In contrast, the Hänscheid model yielded a somewhat lower accuracy rating with a mean of 1.8% and a range of ±7.9%. Therefore, it becomes apparent that the accuracy of TIAC values obtained via the prior-information fitting method, with the 2TPD model as the driving methodology, can be considered relatively satisfactory. This implies that the 2TPD model, in conjunction with the prior information method, offers a robust and dependable approach for determining TIAC values in internal radiation therapy dosimetry.

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REFERENCE

Bergsma, H., Konijnenberg, M. W., van der Zwan, W. A., Kam, B. L. R., Teunissen, J. J. M., Kooij, P. P., Mauff, K. A. L., Krenning, E. P., & Kwekkeboom, D. J. (2016). Nephrotoxicity after PRRT with 177 Lu-DOTA-octreotate. *European Journal of Nuclear Medicine and Molecular Imaging*, *43*, 1802–1811.

Bolch, W. E., Eckerman, K. F., Sgouros, G., & Thomas, S. R. (2009). MIRD pamphlet no. 21: a generalized schema for radiopharmaceutical dosimetry—standardization of nomenclature. *Journal of Nuclear Medicine*, *50*(3), 477–484.

Cherry, S. R., Sorenson, J. A., & Phelps, M. E. (2012). *Physics in nuclear medicine e-Book*. Elsevier Health Sciences.

Devasia, T. P., Dewaraja, Y. K., Frey, K. A., Wong, K. K., & Schipper, M. J. (2021). A Novel Time-Activity Information-Sharing Approach Using Nonlinear Mixed Models for Patient-Specific Dosimetry with Reduced Imaging Time Points: Application in SPECT/CT After 177Lu-DOTATATE. *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine*, *62*(8), 1118–1125. https://doi.org/10.2967/jnumed.120.256255

Gear, J. I., Cox, M. G., Gustafsson, J., Gleisner, K. S., Murray, I., Glatting, G., Konijnenberg, M., & Flux, G. D. (2018). EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations. *European Journal of Nuclear Medicine and Molecular Imaging*, *45*(13), 2456–2474.

Glatting, G., Bardiès, M., & Lassmann, M. (2013). Treatment planning in molecular radiotherapy. *Zeitschrift Für Medizinische Physik*, *23*(4), 262–269.

Glatting, G., Kletting, P., Reske, S. N., Hohl, K., & Ring, C. (2007). Choosing the optimal fit function: Comparison of the Akaike information criterion and the F-test. *Medical Physics*, *34*(11), 4285–4292. https://doi.org/10.1118/1.2794176

Gustafsson, J., & Taprogge, J. (2022). Theoretical aspects on the use of single-time-point dosimetry for radionuclide therapy. *Physics in Medicine & Biology*, *67*(2), 25003.

Hänscheid, H., Lapa, C., Buck, A. K., Lassmann, M., & Werner, R. A. (2018). Dose mapping after endoradiotherapy with 177Lu-DOTATATE/DOTATOC by a single measurement after 4 days. *Journal of Nuclear Medicine*, *59*(1), 75–81.

Hardiansyah, D., Maass, C., Attarwala, A. A., Müller, B., Kletting, P., Mottaghy, F. M., & Glatting, G. (2016). The role of patient-based treatment planning in peptide receptor radionuclide therapy. *European Journal of Nuclear Medicine and Molecular Imaging*, *43*(5), 871–880.

Haug, A. R. (2020). PRRT of neuroendocrine tumors: individualized dosimetry or fixed dose scheme? *EJNMMI Research*, *10*(1), 1–3.

Hou, X., Brosch, J., Uribe, C., Desy, A., Böning, G., Beauregard, J.-M., Celler, A., & Rahmim, A. (2021). Feasibility of single-time-point dosimetry for radiopharmaceutical therapies. *Journal of Nuclear Medicine*, *62*(7), 1006–1011.

Jiménez-Franco, L. D., Glatting, G., Prasad, V., Weber, W. A., Beer, A. J., & Kletting, P. (2021). Effect of tumor perfusion and receptor density on tumor control probability in 177Lu-DOTATATE therapy: An in silico analysis for standard and optimized treatment. *Journal of Nuclear Medicine*, *62*(1), 92–98. https://doi.org/10.2967/jnumed.120.245068

Kam, B. L. R., Teunissen, J. J. M., Krenning, E. P., de Herder, W. W., Khan, S., Van Vliet, E. I., & Kwekkeboom, D. J. (2012). Lutetium-labelled peptides for therapy of neuroendocrine tumours. *European Journal of Nuclear Medicine and Molecular Imaging*, *39*(1), 103–112.

Kletting, P., Schimmel, S., Kestler, H. A., Hänscheid, H., Luster, M., Fernandez, M., Bröer, J. H., Nosske, D., Lassmann, M., & Glatting, G. (2013). Molecular radiotherapy: the NUKFIT software for calculating the time-integrated activity coefficient. *Medical Physics*, *40*(10), 102504.

Maaß, C., Sachs, J. P., Hardiansyah, D., Mottaghy, F. M., Kletting, P., & Glatting, G. (2016). Dependence of treatment planning accuracy in peptide receptor radionuclide therapy on the sampling schedule. *EJNMMI Research*, *6*(1), 1–9.

Miederer, M., Reber, H., Helisch, A., Fottner, C., Weber, M., & Schreckenberger, M. (2012). One single-time-point kidney uptake from OctreoScan correlates with number of desintegrations measured over 72 hours and calculated for the 6.7 hours half-life nuclide 177Lu. *Clinical Nuclear Medicine*, *37*(10), e245–e248.

Siegel, J. A., Thomas, S. R., Stubbs, J. B., Stabin, M. G., Hays, M. T., Koral, K. F., Robertson, J. S., Howell, R. W., Wessels, B. W., & Fisher, D. R. (1999). MIRD pamphlet no. 16: techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose

estimates. *Journal of Nuclear Medicine*, *40*(2), 37S-61S.

Thundimadathil, J. (2012). Cancer treatment using peptides: current therapies and future prospects. *Journal of Amino Acids*, 2012:967347. doi: 10.1155/2012/967347.

Vicini, P., Brill, A. B., Stabin, M. G., & Rescigno, A. (2008). Kinetic modeling in support of radionuclide dose assessment. *Seminars in Nuclear Medicine*, *38*(5), 335–346. https://doi.org/10.1053/j.semnuclmed.2008.05.007