Estimation of main and total effect of PBPK parameters in Meningioma patients

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Abstract. This study aims to identify the most important parameters in the Physiologically-Based Pharmacokinetic (PBPK) model of Peptide Receptor Radionuclide Therapy (PRRT). By knowing the size of the contribution of physiological parameters to the PBPK model, it can reduce the variability of the absorbed dose (AD) in organs at risk, such as the kidney and tumor between individuals. The small variability has the potential to increase the accuracy of planning individual radionuclide therapy treatments. This study uses the extended Fourier Amplitude Sensitivity Test (eFAST) Global Sensitivity Analysis method, the best variance-based global method in analyzing the PBPK model. A whole-body PBPK model that has been developed for treatment planning in PRRT therapy for meningioma patients (n = 7). The parameters of interest analyzed were organ receptor densities $R_{dens}$, organ flows $f$, organ release rates, and peptide binding rate. AD as the desired output from the eFAST algorithm by calculating $S_i$ and $S_{Ti}$ from each AD Kidney and AD Tumor. All parameters of interest are converted into the lognormal distribution. The sampling strategy based on eFAST sampling, the interference factor is equal to 4. To see the convergence of the convergence value of $S_i$ and $S_{Ti}$, a simulation was performed with a total evaluation of 129, 257, 513, 1025, 2049, 4097, and 8193. The results of the simulation, inter-individual variability of tumor AD (coefficient of variation CV up to CV = 73%) was higher than that organ at risk (e.g. kidneys CV around 22%). Based on GSA analysis, the most important parameter determined the AD of tumors, tumors receptor density ($S_i = 0.8, S_{Ti} = 0.93$), kidneys AD was kidneys receptor density ($S_i = 0.66, S_{Ti} = 0.71$). After validating $S_i$ by fixing every parameter considered important, the results can reduce the CV of the kidney AD from 22% to 1%, with a decrease in CV presentation of around 95%. CV AD tumor 1 was reduced by 68% from CV 44% to 14%, and CV in tumor AD 2 from 72% to 17% with a reduced CV presentation of about 77%. It was concluded that receptor measurement is important because it can improve the accuracy of radionuclide therapy treatment.

1. Introduction
Meningioma is a common intracranial nonglial primary neoplasm. Well-differentiated vascular tumor with slow growth and low potential to become invasive, but still possible to become aggressive and malignant [1]. The incidence of meningiomas is about 36% of all brain tumors, the incidence is estimated at 98 / 100,000 people, with an estimated 2:1 ratio between women and men, and the incidence increases with age [2].
About 90% of meningiomas express somatostatin receptors (SSTR), especially receptors with subtypes 1 and 2 [3]. Because it expresses a strong enough SSTR, the meningioma is susceptible to Peptide Receptor Radionuclide Therapy (PRRT) [4]. The potential for PRRT has been recognized in Europe in the latest meningioma treatment guidelines [2]. The only prospective phase 2 trial currently available, 34 patients demonstrated long-term stability at 65.6% with an average overall survival (OS) of 8.6 years [2]. PRRT treatment uses radioactive somatostatin analogues (SSA) to target SSTR on the surface of NET tumor cells or meningiomas [1, 5].

Currently PRRT treatment is still carried out with standard doses, so the potential differences in biodistribution and toxicity between individuals are ignored. Meanwhile, it is known that individual treatment protocols have the potential to increase the effect of targeted internal molecular radiotherapy (mRT) [5]. Through individual-based treatment planning, biokinetics can be calculated and individual patient dosimetry can be calculated so that individual therapeutic biodiversity can be predicted accurately [6–8]. Treatment planning consists of determining the amount of activity to be given at the time of therapy appropriately, with the aim of minimizing the toxicity to organs at risk (OAR) and maximizing the absorbed dose in the tumor [5, 9]. The physiologically based pharmacokinetics (PBPK) model is a very effective tool for simulating the biokinetics of radioactively labeled drugs, and predicting the absorbed dose (AD) of organs during PRRT treatment [10, 11]. The PBPK model has advantages over using the sum of exponential (SOE) function. The PBPK model can describe the processes of substances labeled radioactively based on anatomy and physiological processes, namely administration, distribution, metabolism, and excretion (ADME) such as drug distribution through the bloodstream, specific binding, internalization and degradation, excretion through the kidneys, and physical decay [5, 10].

In internal radiation therapy, the inter-individual variability of internal AD is due to several sources, one of which is biokinetic parameters [12, 13]. These parameters can be measured / estimated before therapy which will affect the determination of activity and absorption dose. To find out the source of variability of the PBPK model, a sensitivity analysis of the contribution of parameters to the variability between AD individuals can be done. Sensitivity analysis examines how variability of model output is related to variability of model inputs [14, 15]. Recent research has been carried out by Sobol's Global Sensitivity Analysis (GSA) method in identifying the effect of inter-individual variability for the calculation of AD organ $^{18}$F-FSPG using the MIRD formula, from this study showing that the determination of the Time Integrity Activity Curve (TIAC) is proven to reduce the variability between individuals, individual organ AD in the population (about 90% for inter-individual variability of AD kidney based on the $S_i$, main effect) whereas $S$-value contributed little (less than 10% for AD kidney) [12]. In the PBPK model, the GSA method is appropriate because it will interfere with all input parameters of interest in each sampling step and take into account the interactions between parameters [15]. In addition, a research on sources of variability among TIAC individuals on the PBPK model for $^{177}$Lu-labeled PSMA-targeting radioligands using the GSA method extended Fourier Amplitude Sensitivity Test (eFAST), this study shows the three most important parameters that affect inter-individual variability based on the the largest $S_i$ and $S_{ij}$ value, namely blood flow to the kidney $f_k$, the density of the kidney receptors [$R_{k0}$] and the rate of drug release from the kidney ($\lambda_{K_{release}}$) [13].

Identification of the important parameters of the PBPK model that affect the variability between individuals is necessary to individualize treatment planning in nuclear medicine [5, 13]. Therefore, in this study, we performed the eFAST method of GSA to identify the physiological parameters of the PBPK model that have a major contribution to the inter-individual variability of AD kidneys and tumors on $^{90}$Y-DOTATATE (PRRT) therapy. eFAST is a variance-based GSA method that does not depend on any assumptions regarding the structure of the model (does not depend on assumptions regarding the functional relationship between model outputs and inputs), besides that it only requires less number of evaluations when compared to other variant-based GSA methods, such as Sobol [15]. This study was conducted in a simulation manner that shows the most important parameters identified by the eFAST GSA that affect inter-individual variability in AD kidneys and tumors.
2. Method

2.1. Data and Tools
Quantitative sensitivity analysis is carried out computationally. The equipment used is a computer that has MATLAB r2018b installed for modeling and simulation. This study uses secondary data from research Kletting et al., 2016 [9]. There were 12 parameters (Table 1) that were tested for the sensitivity analysis. These parameters were taken from supplement A [9].

2.2. Structure PBPK model for PRRT
The PBPK model for PRRT that has been developed by Kletting et al. 2012 [10] describes the main mechanisms of radiolabeled peptide, namely, distribution through the bloodstream, specific binding, internalization, degradation, physical decay, and excretion via the kidneys. Liver, spleen, kidney, and tumor tissue are modeled explicitly, other tissues / organs are combined into "rest". The kidney is modeled explicitly because it includes OAR, the kidney expresses SST2 and unspecific uptake (not completely covered by amino acids) [10,16]. The tumor and spleen are modeled explicitly due to the high density of SST2 and total accumulation of radiolabeled peptides [10, 17]. A liver that is ten times larger than the spleen, but a SST2 density five times lower than the spleen is modeled explicitly due to the high total receptor count [10,17]. Furthermore, this model includes uptake and release of unspecified intact peptide from the kidney into serum. The competition between labeled and unlabeled pharmacists in the PBPK model is divided into two circulatory subsystems with the same physiological parameters [5,10]. Model development includes the creation and arrangement of compartments, each compartment contains parameters and equations related to the radiopharmaceutical process based on ADME physiology, these equations are made in the tools rules in Symbiology.

2.3. Parameters Sampling

| Parameter         | Definition                           | Normal Distribution | Lognormal Distribution |
|-------------------|--------------------------------------|---------------------|------------------------|
| $[R_{K,0}]$       | Receptor density in kidney           | 7.00 1.34           | 1.93 0.19              |
| $[R_{S,0}]$       | Receptor density in spleen           | 10.50 3.27          | 2.31 0.30              |
| $[R_{L,0}]$       | Receptor density in liver            | 1.41 0.61           | 0.26 0.41              |
| $[R_{REST,0}]$    | Receptor density in rest             | 0.51 0.18           | -0.72 0.34             |
| $[R_{TU1,0}]$     | Receptor density in tumor1           | 19.00 8.04          | 2.86 0.41              |
| $[R_{TU2,0}]$     | Receptor density in tumor2           | 16.55 11.69         | 2.60 0.64              |
| $\lambda_{NT,\text{release}}$ | Release rate in normal tissue       | 0.00 0.00           | -9.50 0.48             |
| $\lambda_{TU1,\text{release}}$ | Release rate in tumor 1              | 0.00 0.00           | -8.77 0.40             |
| $\lambda_{TU2,\text{release}}$ | Release rate in tumor 2              | 0.00 0.00           | -9.13 0.08             |
| $f_{TU1}$         | Serum flow rate to tumor 1           | 0.34 0.42           | -1.52 0.95             |
| $f_{TU2}$         | Serum flow rate to tumor 2           | 0.50 0.41           | -0.95 0.72             |
| $k_{Pr}$          | Binding rate peptide to serum        | 0.00 0.00           | 1.38 0.25              |

The twelve physiological parameters of interest are shown in Table 1 consisting of receptor density $[R_{d}]$ of kidney, spleen, liver, tumors 1 and 2, rest organs, serum flow rate to tumor $[f_{tu}]$ for tumor 1 and
tumor 2, rate of degradation. \([\lambda_{\text{release}}]\) tumor 1, tumor 2 and normal tissue, binding of the peptide rate to serum \([k_p]\). Parameters with normal distribution are modified to log-normal distribution to avoid negative mean values because physiological parameters are not recommended to be negative. Equations 2.1 and 2.2 are the equations used in converting the mean and standard deviation of the normal distribution to the log-normal distribution:

\[
\text{mean}_{\text{logn}} = 2 \times \ln(\text{mean}_{\text{normal}}) - 0.5 \times \ln(\text{mean}^2_{\text{normal}} + SD^2_{\text{normal}})
\] (2.1)

\[
SD_{\text{logn}} = \sqrt{(-2 \times \ln(\text{mean}_{\text{normal}}) + \ln(\text{mean}^2_{\text{normal}} + SD^2_{\text{normal}}))}
\] (2.2)

2.4. eFAST Method
The variance partitioning in eFAST works by varying different parameters at different frequencies, matching the parameter identities in their variation frequencies. Fourier analysis then measures the frequency strength of each parameter in the model output. Thus, how strongly the parameter frequency propagates from the input, through the model, to the output serves as a measure of the model’s sensitivity to the parameter [18]. eFAST sampling uses equations that are more efficient in model evaluation [19]:

\[
x_i = \frac{1}{2} + \frac{1}{\pi} \arcsin(\sin \omega_i s + \varphi_i)
\] (2.3)

where \(\bar{x_i}\) is the value of the factor \(i\), \(\varphi_i\) is the uniformly selected random phase-shift in \((0, 2\pi)\), \(s\) varies in \((-\pi/2, \pi/2)\). The advantage of using Equation (2.1) is that the starting point of the curve can be anywhere in \(K^n\) space. In the resampling scheme, the sample size is defined as:

\[
N_s = (2M \omega_{\text{max}} + 1)N_r
\] (2.4)

where \(M\) is the interference factor (with a value of 4), \(\omega_{\text{max}}\) is the largest of the frequency sets \(\omega_t\). \(N_r\) indicates the number of curves used. The frequency-based sampling method for eFAST GSA as suggested in the literature uses the following Number of Model Evaluation.

| \(N_s\) | \(\omega_t\) | Max (\(\omega_{-t}\)) | Step | \(\omega_1\) | \(\omega_2\) | \(\omega_3\) | \(\omega_4\) |
|--------|--------------|---------------------|------|-------------|-------------|-------------|-------------|
| 65     | 8            | 1                   | 0    | 1           | 8           | 1           | 1           |
| 129    | 16           | 2                   | 1    | 1           | 16          | 1           | 2           |
| 257    | 32           | 4                   | 1    | 1           | 32          | 3           | 2           |
| 513    | 64           | 8                   | 1    | 5           | 64          | 3           | 6           |
| 1025   | 128          | 16                  | 2    | 9           | 128         | 5           | 11          |
| 2049   | 256          | 32                  | 4    | 17          | 256         | 9           | 21          |
| 4097   | 512          | 64                  | 8    | 33          | 512         | 17          | 41          |
| 8193   | 1024         | 128                 | 16   | 65          | 1024        | 33          | 81          |

Note: \(\omega_2\) is assumed to be the frequency of the interest parameter \(\omega_t = \omega_2\)

Main effect \(S_i\) is calculated by the ratio of \(\frac{\delta_i}{D}\), the estimated main effect of \(x_i\) on \(y\). While the total effect is \(S_T = 1 - S_i\). \(\delta_i, D\) is determined by the equation:
\[ D_i = \sum_{p=1}^{M} \frac{A_{p \omega_i}}{(N_e-1)/2} \]  

\[ D = \sum_{j=1}^{N_q} A_j \]  

Where \( A_j = A_j^2 + B_j^2 \)  

\[ A_j = \begin{cases} \frac{1}{N_q} \left[ f(sN_o + q) + \sum_{q=1}^{N_q} [f(sN_o + q) + f(sN_o - q)] \times \cos \left( j \frac{\pi}{N_q} \right) \right] & \text{if } j \text{ even} \\ 0, & \text{if } j \text{ odd} \end{cases} \]  

\[ B_j = \begin{cases} 0, & \text{if } j \text{ even} \\ \frac{1}{N_q} \left[ \sum_{q=1}^{N_q} [f(sN_o + q) - f(sN_o - q)] \times \sin \left( j \frac{\pi}{N_q} \right) \right] & \text{if } j \text{ odd} \end{cases} \]  

where \( N_q = (N'_q - 1)/2 \) dan \( N_o = (N'_o + 1)/2 \), \( N'_q = (N'_q + 1)/2 \) 

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**Figure 1.** Research Work flow Chart.
The variance-based methods $S_i$ and $S_{T_i}$ are in the range [0.1]. Input factors with a sensitivity metric value close to 1 are significant for the output variable. The condition that the input factor has no effect when $S_{T_i} = 0$. Note that, eFAST is always $S_i \leq S_{T_i}$, and the difference between $S_i$ and $S_{T_i}$ indicates the interaction effect on the model output. The following is a chart of the research workflow carried out (Figure 1).

3. Results and Discussion

3.1. Sample Validation

The frequency distribution of the data used is a major factor determining the type of statistical analysis that can be performed validly on any data set. In this study, the sampling method for 12 parameters was carried out using a log-normal distribution to avoid negative values for the parameter of interest, this is a consequence of the PBPK model, a physiological modeling method, where there are no negative physiological parameters. Skewed distribution is very common when the average value is low, the variance is large, and the value cannot be negative [20]. Sampling was carried out in 8193 iterations until it converged.

![Image of parameter histograms](a)(b)(c)(d)

**Figure 2.** Example of Parameter Sampling: (a) Parameter Histogram [Rd$_K$], (b) Parameter Histogram [Rd$_L$], (c) Parameter Histogram [Rd$_{TU1}$], (d) Parameter Histogram [Rd$_{TU2}$].

Validation of the sample produced through the simulation is done by visually observing the histogram form of each parameter and comparing the value of the Coefficient of Variation (CV) of each calculated parameter. The results of the histogram (Figure 2) of each parameter show the shape of the log-normal distribution and the CV of the simulation results parameters do not differ much from the CV from literature sources. Based on Table 3, the largest deviation between the two in the $\lambda_{TU2}$
parameter, the release is 5.40% for other parameters ranging from 0 to 2%. Thus the sampling method used is well validated because it has almost the same values.

### Table 3. CV deviation based on literature with CV simulation results

| No | Parameter | Unit | Literatur | Simulasi | Deviasi CV<sub>L</sub> & CV<sub>S</sub> |
|----|-----------|------|-----------|----------|----------------------------------------|
|    |           |      | MEAN      | SD       | CV<sub>L</sub> (%) | MEAN | SD | CV<sub>S</sub> (%) |
| 1  | [R<sub>E1</sub>] | [nmol.L<sup>-1</sup>] | 7.00 | 1.34 | 19 | 6.99 | 1.33 | 19 | 0.38 |
| 2  | [R<sub>E2</sub>] | [nmol.L<sup>-1</sup>] | 10.50 | 3.27 | 31 | 10.52 | 3.25 | 31 | 0.69 |
| 3  | [R<sub>L1</sub>] | [nmol.L<sup>-1</sup>] | 1.41 | 0.61 | 43 | 1.41 | 0.60 | 43 | -0.06 |
| 4  | [R<sub>REST</sub>] | [nmol.L<sup>-1</sup>] | 0.51 | 0.18 | 34 | 0.51 | 0.17 | 34 | 0.95 |
| 5  | [R<sub>T1,0</sub>] | [nmol.L<sup>-1</sup>] | 19.00 | 8.04 | 42 | 18.98 | 8.10 | 43 | -0.82 |
| 6  | [R<sub>T2,0</sub>] | [nmol.L<sup>-1</sup>] | 16.55 | 11.69 | 71 | 16.83 | 11.64 | 69 | 2.11 |
| 7  | λ<sub>TU,release</sub> | [min<sup>-1</sup>] | 8.43E-05 | 4.28E-05 | 51 | 8.46E-05 | 4.40E-05 | 52 | -2.45 |
| 8  | λ<sub>TU1,release</sub> | [min<sup>-1</sup>] | 1.69E-04 | 6.99E-05 | 41 | 1.68E-04 | 6.79E-05 | 40 | 2.42 |
| 9  | λ<sub>TU2,release</sub> | [min<sup>-1</sup>] | 1.31E-04 | 9.06E-05 | 69 | 1.30E-04 | 8.50E-05 | 65 | 5.40 |
| 10 | f<sub>TU1</sub> | [ml.min<sup>-1</sup>.g<sup>-1</sup>] | 0.34 | 0.42 | 121 | 0.33 | 0.41 | 125 | -2.72 |
| 11 | f<sub>TU2</sub> | [ml.min<sup>-1</sup>.g<sup>-1</sup>] | 0.50 | 0.41 | 82 | 0.49 | 0.41 | 84 | -1.74 |
| 12 | k<sub>p</sub> | [min<sup>-1</sup>] | 0.00 | 0.00 | 26 | 4.11E-04 | 1.05E-04 | 26 | 1.10 |

CV<sub>L</sub> = CV obtained based on literature data
CV<sub>S</sub> = CV generated from simulation

### 3.2. Coefficient of Variation (CV) AD Kidneys and Tumors

The results of our computational calculations, the mean ± SD of each AD in kidney, tumor 1, and tumor 2 was (17.5 ± 13.8) Gy, (126.14 ± 55.25) Gy, and (216.06 ± 157.08) Gy, with the coefficient of variation (CV) ie the ratio of SD to mean in tumor AD is greater than CV in kidney AD by 22%, 44%, and 73% for kidney, tumor 1, and tumor 2. Distribution of renal AD, tumor 1, and tumor 2 can be seen in Figure 3.2. From the results of this study, it can be seen that the variability between individuals is quite large, so individual-based treatment planning is very important to do, because each patient has different body conditions, levels of toxicity, biodistribution, anatomy and physiology of organs. Our results are not much different from those of Zvereva et al., [12], of the five volunteers have an organ CV of 10% -57%. The same thing with research from Hardiansyah et al. [13], of the 13 patients, 31% had renal CV AD, and for tumors it reached 59%.

From the CV value above, it is clear that if treatment is carried out with a fixed dose, in which all patients are considered to have the same condition so that the dose given is the same, of course the treatment is less optimal. If the patient receives an incorrect or inaccurate dose, there will be two possibilities that will occur, namely the patient will receive an excessive dose which is very dangerous to OAR, or the second patient will receive a smaller dose than it should be, if it happens of course, will affect the efficacy of the treatment.

However, we know that making individual-based measurements requires considerable time and effort to measure all physiological parameters, therefore it is necessary to identify the most important physiological parameters that affect the inter-individual variability of organ AD. If the most important parameters are known, then the individual-based treatment planning process will be easier to do, because it only measures the most important physiological parameters. It takes less time, cost and effort. Therefore, it is very necessary to carry out quantitative analysis, global sensitivity analysis (GSA) to the physiological parameters of the PBPK model.
3.3. The convergence of \( S_i \) and \( S_{Ti} \)

The eFAST simulation produces a number of main effect (\( S_i \)) and total effect (\( S_{Ti} \)) calculations for each parameter. \( S_i \) is the main effect of the parameter of interest \( i \), if the "true" value of the parameter of interest \( i \) is known, it will reduce the amount of variability between individuals. \( S_{Ti} \) is the total effect of the parameter of interest \( i \), representing the portion of the remaining variance if all parameters \( \sim i \) (except \( i \)) are known to be "true" values. The maximum number of evaluations suggested by A. Saltelli et al.,[19] is 8193 sample data, to ensure the convergence of \( S_i \) and \( S_{Ti} \) calculations for each of these parameters. The number of samples used in stages ranging from 129, 257, 513, 1025, 2049, 4097, to 8193. The graph of the convergence of \( S_i \) and \( S_{Ti} \) of each organ can be seen in Figure 3.3.

Figures 3.3 (a) and (b) are a graph of the convergence of \( S_i \) and \( S_{Ti} \) parameters that affect AD kidney, when viewed from the graph, the green line followed by a black dot (the boundary of the number of evaluations) describes the parameter \([R_{K,0}]\) tends to be constant from the initial evaluation count. The graph shows that the receptor density of the kidney \([R_{K,0}]\) is the most important parameter for AD kidneys. Thus \([R_{K,0}]\) has a strong influence on the inter-individual variability of renal AD. Based on the definition of \( S_i \), if the "true" value of \([R_{K,0}]\) is known, there will be a change in the CV AD value of the kidney to be smaller than before.

Furthermore, Figures 4.3 (c) and (d) are convergence graphs of \( S_i \) and \( S_{Ti} \) for the most important parameters based on the results of quantitative sensitivity analysis based on eFAST variance, from the graphs of both \( S_i \) and \( S_{Ti} \) shows that the most important parameter that affects AD tumor1 is the tumor receptor density 1, \([R_{TU1,0}]\). The resulting \( S_i \) and \( S_{Ti} \) values are quite large, almost close to 1, and the difference between the \( S_i \) and \( S_{Ti} \) receptor density 1 tumor values with other parameters that are
considered to affect AD tumor-1 is quite far, from here it indicates that [RTU1,0] is very important to know the “true” value.

The final graphs Figure 3.3 (e) and (f) show the convergence of the main and total effects that affect inter-individual variability for AD tumor 2. Graphic (e) is the main effect of AD tumor 2 showing convergence starting from the number of evaluations 513. The resulting Si value is close to 1, and the difference with the Si value of other parameters that are considered important is quite large. From the results of the eFAST analysis, the most important parameter that had the most influence on the inter-individual variability of AD tumor 2 was the receptor density tumor 2 [R_{TU2,0}]. Likewise, the total effect (S_{Ti}) generated from the eFAST analysis shows that the most important parameter is the receptor density tumor 2 [R_{TU2,0}].
Based on the $S_i$ and $S_T$ convergence charts (Figure 3.3), the measurement of receptor density for each AD organ for both kidney, tumor 1 and tumor 2 is highly recommended to be carried out accurately during the treatment planning process. So that the amount of activity and the dose given is right, not excessive and not deficient. With the hope that the dose will be effective in killing the tumor, but OAR is still protected.

Details of $S_i$ and $S_T$, calculations for all parameters of interest in kidney AD, tumor 1, and tumor 2 can be seen in Table 4 and Table 5, the most influential parameter for kidney AD is the receptor density for the kidney $[R_{K,0}]$ with the value of $S_i = 0.6611$ and $S_T = 0.71$, followed by the second most important parameter, namely the release rate in normal tissue $S_i = 0.2875$ and $S_T = 0.32$. The rational result is because biologically the kidney has the same type of receptor as a meningioma tumor, namely SST2 is present, the peptide receptors in this organ are the first gates to bind and enter drugs into its cells along with the process of competition for free receptors. so it is perfectly normal to make it the most important parameter to measure carefully. The same thing happened to AD tumors 1 and 2, the simulation results state that the most important parameter of receptor density is tumor 1 $[R_{TU1,0}] S_i = 0.7935$ and $S_T = 0.90$ and tumor 2 $[R_{TU2,0}] S_i = 0.8025$ and $S_T = 0.93$.

There are no parameters other than those mentioned above with the condition $S_T = 0$, which means it is a noninfluential parameter. However, all parameters other than those mentioned above, in each organ other than the whole body are in a condition where the value $S_T \equiv 0$ means that these parameters can be set at any value within the distribution range without significantly affecting AD variance.

| AD | $S_i$ | $S_T$ |
|----|-------|-------|
| | $[R_{K,i}]$ | $[R_{L,i}]$ | $[R_{REST,i}]$ | $[R_{TU1,i}]$ | $[R_{TU2,i}]$ | $\lambda_{ST,release}$ | $\lambda_{TU1,release}$ | $\lambda_{TU2,release}$ | $f_{TU1}$ | $f_{TU2}$ | $k_f$ |
| Kidney | 0.6611 | 0.0001 | 0.0004 | 0.0016 | 0.0000 | 0.0000 | 0.2875 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| TU1 | 0.0001 | 0.0000 | 0.0001 | 0.0004 | 0.7935 | 0.0000 | 0.0000 | 0.0884 | 0.0000 | 0.0086 | 0.0000 | 0.0000 |
| TU2 | 0.0000 | 0.0000 | 0.0000 | 0.0001 | 0.8025 | 0.0000 | 0.0000 | 0.0535 | 0.0000 | 0.0001 | 0.0000 | 0.0000 |

| AD | $S_i$ | $S_T$ |
|----|-------|-------|
| | $[R_{K,i}]$ | $[R_{L,i}]$ | $[R_{REST,i}]$ | $[R_{TU1,i}]$ | $[R_{TU2,i}]$ | $\lambda_{ST,release}$ | $\lambda_{TU1,release}$ | $\lambda_{TU2,release}$ | $f_{TU1}$ | $f_{TU2}$ | $k_f$ |
| Kidney | 0.71 | 0.01 | 0.01 | 0.01 | 0.00 | 0.01 | 0.32 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| TU1 | 0.04 | 0.04 | 0.04 | 0.04 | 0.90 | 0.04 | 0.04 | 0.14 | 0.04 | 0.07 | 0.04 | 0.04 |
| TU2 | 0.06 | 0.06 | 0.06 | 0.07 | 0.06 | 0.93 | 0.06 | 0.06 | 0.14 | 0.06 | 0.07 | 0.07 |

### 3.4 Validity $S_i$

After the most important parameters of each organ AD were identified then validation was carried out, by comparing the CV results from the initial AD before fixation on each of the most important parameters, to the CV value after fixation. Fixation is done by setting the value of the most important parameter to a certain value, in this study we used the mean value of these parameters (Table 6). In AD kidneys it was identified that the most important parameter is $[R_{K,0}]$, after fixing $[R_{K,0}]$ and simulated, it can reduce CV from 22% to 1%, with a decrease in CV percentage of about 95%. The same was done to validate $S_i$ calculations in AD tumor 1 and tumor 2 by fixing the parameter values $[R_{TU1,0}]$ and $[R_{TU2,0}]$, after simulating the CV of AD tumor 1 was reduced by about 68% from CV 44% to 14. %, and CV in AD tumor 2 from 72% to 17% with a decreased CV presentation of about 77%. Comparison of variability between individuals can be seen in Table 6. Through CV analysis before and after fixation, the percentage reduction in CV, against $CV_R$ with $S_i$ was obtained. So it can be said that the variance-based quantitative GSA was successful.
Table 6. $S_i$ validation on changes in the value of CV

| AD Organ | Parameter | No. Urut Parameter | CV_i (%) | CV_R (%) | $S_i$ | % Deviasi CV_i dan CV_R |
|----------|-----------|--------------------|----------|----------|------|------------------------|
| Kidney   | R dens K  | 1                  | 21.82    | 1.05     | 66.11| 95                     |
| TU_1     | R dens TU_1 | 5               | 43.87    | 14.26    | 79.35| 68                     |
| TU_2     | R dens TU_2 | 6               | 72.67    | 17.02    | 80.25| 77                     |

Note:
- CV_i is the CV value of the AD organ before fixation on the most important parameter
- CV_R is the CV value of organ AD after fixation on the most important parameter

4. Conclusion

This study has demonstrated the implementation of global sensitivity analysis (GSA) using the eFAST method for the whole body PBPK model developed for the $^{90}$Y-labeled PRRT radionuclide therapy. GSA was performed to identify the most important parameters for individualizing the AD calculations in the organ at risk of the kidney and tumor lesions during treatment planning. GSA results of the eFAST method, the most important physiological parameters that affect inter-individual variability in renal AD and tumor lesions, namely kidney receptor density, tumor receptor density 1 and 2. The results of the main effect $S_i$ identification were validated by assigning each of the most important parameter values to a certain value, the validation succeeded in reducing the variability of renal CV AD from 22% to 1%, CV AD tumor 1 from 43% to 14%, and CV AD tumor 2 from 72% to 17%. These results can be considered when measuring before therapy to increase the accuracy of the dose received by the patient so that the organs at risk remain protected but can still kill the tumor lesion. However, the results of this study need to be further analyzed qualitatively, this research can be used as a basis or support for research in other fields of science, for example from the side of biology, medicine, pharmacy.

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