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Mathematical Modeling of ^{177}Lu-DOTATATE for Neuroendocrine Tumor Treatment

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Abstract Nowadays, cancer treatment with radiopharmaceuticals is an alternative option for patients who do not respond to treatment with other methods, such as surgical treatment, chemotherapy, or external beam radiotherapy. The ^{177}Lu-DOTATATE is a type of theranostic radiopharmaceutical used to treat neuroendocrine tumor (NETs) patients. This research's objectives were to develop a mathematical model for treating NETS patients with ^{177}Lu-DOTATATE and estimate the appropriate parameters of the model to determine the changes of ^{177}Lu-DOTATATE in the patient's body. The ^{177}Lu-DOTATATE can deliver into cancer cells and organs throughout the body, considered two models, Model I and Model II. They have a similar dynamical compartment structure, but the ^{177}Lu-DOTATATE eliminated from the tumor is different between the two models. This research considers the appropriate parameters for each model to find the solution of the system of ordinary differential equations of each model according to the 4th Runge-Kutta method. The results of Model I and II tend to change ^{177}Lu-DOTATATE in tumors and organs according to the results obtained in mice. After a mathematical model for rearing NETs patients with ^{177}Lu-DOTATATE was developed, it will help the physicians to analyze as the guidelines for treating NETs patients, which is more effective.

MSC: 49K35; 47H10; 20M12
Keywords: ^{177}Lu-DOTATATE; mathematical model of ^{177}Lu-DOTATATE for neuroendocrine tumor treatment; neuroendocrine tumor

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1. Introduction

Neuroendocrine tumors (NETs) are rare tumors, which probably develop at any part and can generate several types of peptides, especially on serotonin. This peptide leads to the incidence of metastatic disease that results in carcinoid heart disease [1–4]. Statistically, the incidence of these tumors is accounted for only 0.5% of all fatalities. In addition,

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approximately 2 per 100,000 women are under 50 years. The main primary sites are the digestive system and the lungs, around 62-67% and 22-27%, respectively [5, 6]. NETs are developed by specialized cells in the neuroendocrine system. These cells have traits of both hormone-producing endocrine cells and nerve cells. They are found throughout the body organs and help to control the human body functions. Besides, hormones are chemical substances carried through the bloodstream to have a specific effect on the activity of the other organs or cells in the body. All NETs are considered as malignant tumors [2, 7].

There are several ways to treat NETs patients, such as surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy, and immunotherapy [8, 9]. However, the recent successful method is called Peptide Receptor Radionuclide Therapy (PRRT). It becomes a specific treatment that uses radiolabeled peptides for recovering NETs patients. This is an essential therapy for patients who do not respond to other treatments [10]. The PRRT considers down to the target molecules of the cancer cells and determines the appropriate radiopharmaceuticals to bind with the receptors on the cell walls of the cancer cells. This process can directly cure patients in an accurate position [11, 12].

One of the radiopharmaceuticals called [^{177}Lu-DOTA^0, Tyr^3] octreotate (^{177}Lu-DOTATATE) is receiving great attention for PRRT treatment to treat NETs patients. This is because it can directly attack and destroy NETs cells in different locations of the human body [13]. The mechanism of ^{177}Lu-DOTATATE works with cancer cells is shown in Figure 1. Another advantage of using ^{177}Lu-DOTATATE is that physicians can observe the flow of the substance through the Single-Photon Emission Computed Tomography (SPECT) and together with Computed Tomography (CT), which use to scan the components of the body organs [11, 12, 14]. With SPECT/CT, it can help to follow treatment results conveniently and precisely. The high-quality SPECT/CT imaging can help doctors diagnose the disease at the beginning stage to manage more effective treatment for specific patients. Currently, there is no public data on the use of ^{177}Lu-DOTATATE in patients. Several institutions in Thailand, including King Chulalongkorn Memorial Hospital (KCMH), Siriraj Hospital, Ramathibodi Hospital, and Chulabhorn Hospital, provide ^{177}Lu-DOTATATE treatment for NETs, allowing the radiopharmaceutical therapy treatment more interesting and well-known

However, the follow-up with the SPECT/CT treatment is somewhat limited. For example, the high-cost examination leads to the restriction of the treatment cycle in each patient. The consequence is that the diagnosis of the results cannot illustrate all time intervals. This makes physicians cannot determine the substances in the patient body continuously [15, 16]. Practically, when the ^{177}Lu-DOTATATE is administered into the patient's body, it will not only uptake to NETs but also various normal organs such as the stomach, pancreas, adrenal, lungs, intestine, kidneys, femur, spleen, salivary gland, heart, and liver, respectively.

The optimal amount of ^{177}Lu-DOTATATE per cycle should be thoroughly estimated to avoid side effects. The substance that enters the tumor with an insufficient dose cannot inhibit the growth of the tumor. As a result, the treatment of patients is not as effective as it should be. On the other hand, if the amount of administered activity per cycle is too high, it can negatively affect the critical organ such as kidneys and liver [17, 18]. So, it is important to detect or help predict the transportation of ^{177}Lu-DOTATATE in the human body.

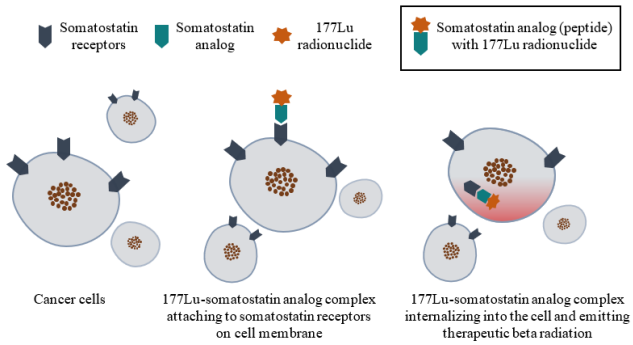


FIGURE 1. The mechanism of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy PRRT for somatostatin -receptor-positive neuroendocrine tumors.

The mathematical model becomes a useful tool and plays a key role in solving this undetectable situation. The mathematical model is abstract structures that use mathematical concepts to describe and develop a behavior system. A solution from the model can be interpreted to the real situation and predict the results for the real-world problems [19]. In the medical field, some mathematical models are used to describe the dynamic of drug diffusion in the circulatory system and tissues in the human body [20]. Another example is using models to optimize the drug release in the patients body [21].

Therefore, this research will focus on the diffusion of ^{177}Lu-DOTATATE in NETs patients through the model. We aimed to develop mathematical models for ^{177}Lu-DOTATATE transportation with different assumptions to predict the trend kinetics of ^{177}Lu-DOTATATE and is used to explain the biodistribution of ^{177}Lu-DOTATATE in NETs patients. Then we explored the concentration and the kinetics in each human organ in the continuous-time in the interval. Finally, the two models are compared to the results and determined which situation is more suitable for model formulation.

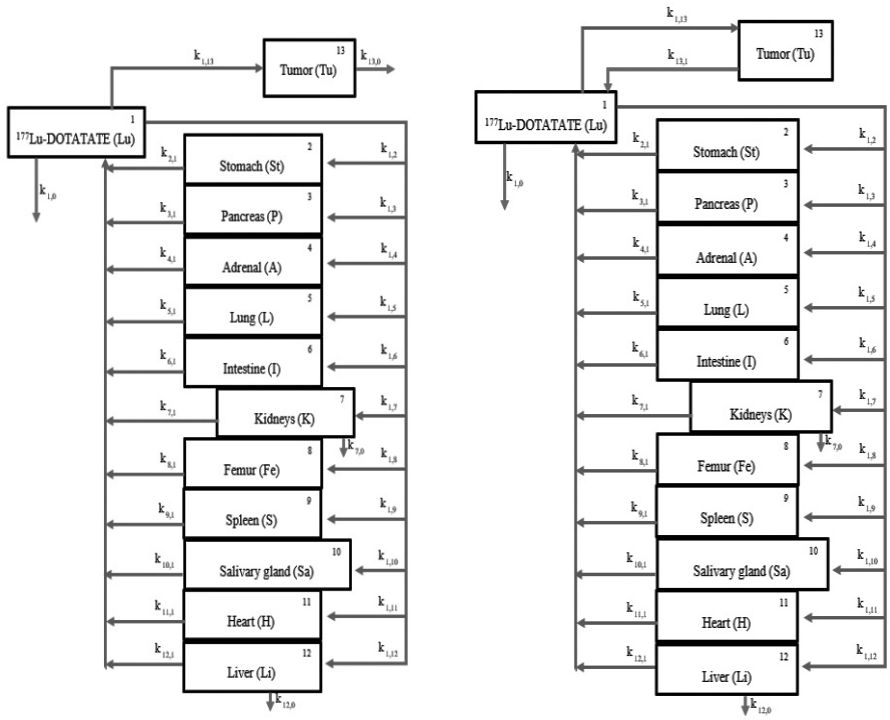
2. Materials and Methods

2.1. ^{177}Lu-DOTATATE transportation in the patients body

The pattern of ^{177}Lu-DOTATATE circulates in the patients body begins when the radiopharmaceutical was injected into the vein system. After that, the substance flows through tumor cells and destroys them, then the concentration of ^{177}Lu-DOTATATE loss from the system. Furthermore, some substances also move to various organs in the patients body, such as the stomach, pancreas, adrenal, lung, intestine, kidneys, femur, spleen, salivary gland, heart, and liver, and it turns back to the blood system. However, kidneys and liver can excrete some of the substance from the body instead of returning to the blood [22–24]. Hence, the compartmental model for this transportation (Model I) is shown in Figure 2(a).

Nevertheless, the concept of the transportation of ^{177}Lu-DOTATATE in the human body in some research has a different point. According to Kenneths work, the substance's concentration can remove to the blood vessel after tumor destruction, and it does not

produce a loss or out of the system [25]. Therefore, the compartment model following (Model II) this situation is shown in Figure 2(b).



(a) Model I **(b) Model II**

FIGURE 2. *The compartmental model for* ^{177}*Lu-DOTATATE flow in human body (a) in the case of the radiopharmaceutical loss after tumor destruction (Model I),(b) the radiopharmaceutical return to the blood system (Model II).*

2.2. MATHEMATICAL MODELS FOR THE DYNAMICS OF ^{177}LU-DOTATATE

From these two compartmental models, we develop two mathematical models by referring to the research of M. Mousavi-Daramoroudi. Their study focuses on the simulation on the transportation of ^{177}Lu-DOTATOC in mice since the flow of this radiopharmaceutical has nearly the same characteristics with ^{177}Lu-DOTATATE that uses in NETs patient treatment [23, 26]. They only study transportation in the blood system, such as the heart, lungs, intestine, bone, spleen, stomach, muscles, liver, and kidneys. However, tumors are not considered of the flow of this work [23]. Another research on studying the distribution of ^{177}Lu-DOTATATE interests the additional organs, such as the pancreas, adrenal, femur, salivary gland, and tumors in mice [24].

There are following these assumptions and the compartmental models. The concentration of ^{177}Lu-DOTATATE in the human body starts with the dose that the doctors specifically give to patients. It then flows into tumor cells and the eleven organs with different concentration rates and turns back to the blood system with the constant mice.

Moreover, some amount of ^{177}Lu-DOTATATE is removed before reaching the tumor cells and organs. Hence, the rate of change of ^{177}Lu-DOTATATE in patients can be expressed as the following equation.

$$\begin{aligned}\frac{dLu(t)}{dt} =& -k_{1,0}Lu(t) - k_{1,2}Lu(t) - k_{1,3}Lu(t) - k_{1,4}Lu(t) - k_{1,5}Lu(t)\\ &- k_{1,6}Lu(t) - k_{1,7}Lu(t) - k_{1,8}Lu(t) - k_{1,9}Lu(t) - k_{1,10}Lu(t)\\ &- k_{1,11}Lu(t) - k_{1,12}Lu(t) - k_{1,13}Lu(t) + k_{2,1}St(t) + k_{3,1}P(t)\\ &+ k_{4,1}A(t) + k_{5,1}L(t) + k_{6,1}I(t) + k_{7,1}K(t) + k_{8,1}Fe(t)\\ &+ k_{9,1}S(t) + k_{10,1}Sa(t) + k_{11,1}H(t) + k_{12,1}Li(t)\end{aligned} \tag{2.1}$$

The notations and their meanings in the above equation are part of the variable and the parameter. $Lu(t)$ is the percentage of injected activity per gram of tissue (%IA/g) of ^{177}Lu-DOTATATE given to the mice and the variable $St(t)$, $P(t)$, $A(t)$, $L(t)$, $I(t)$, $K(t)$, $Fe(t)$, $S(t)$, $Sa(t)$, $H(t)$, $Li(t)$ and $Tu(t)$ are the percentage of injected activity per gram of tissue (%IA/g) of ^{177}Lu-DOTATATE in stomach, pancreas, adrenal, lung, intestine, kidneys, femur, spleen, salivary gland, heart, liver and tumor, respectively. The notations and their meanings of parameters are shown in Table 1.The compartment model's order is represented by n, as shown in Figure 2(a) and 2(b).

TABLE 1. The parameters and their descriptions.

Parameters	Descriptions	Unit
$k_{n,0}$	The rate of concentration of removal constant from organ n to extra.	1/hr.
$k_{1,n}$	The rate of concentration from blood to the organ n .	1/hr.
$k_{n,1}$	The rate of concentration from organ n to the body fluids.	1/hr.

However, the notation represents the percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE at different parts by calculating the following formula [27].

$$\%IA/g_{mice} = \frac{A_{Tmice}M_{Tmice}}{A_{inj}} \cdot 100\% \tag{2.2}$$

where, $A_{Tmice}$is the concentrated activity on sample tissue in mice, $M_{Tmice}$is mass of sample tissue in mice and $A_{inj}$is total injected activity to mice.
The percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE in mice was converted to the percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE in humans using the following formula [28].

$$\%IA/organ_{human} = [\%IA/g_{mice} \cdot M_{mice}(kg)] \cdot \left(\frac{m(g)}{M(kg)}\right)_{human} \tag{2.3}$$

where, $\%IA/organ_{human}$ is the percentage of injected activity per organ in human, $\%IA/g_{mice}$ is the percentage of injected activity per gram in mice, m is the organ mass and M is the total body weight.

The pattern of change of ^{177}Lu-DOTATATE is generally considered in the half-life value of ^{177}Lu-DOTATATE, it has a half-life of approximately 6.71 days [29]. However,

the ^{177}Lu-DOTATATE changes in the patient's body probably not depend on the half-life value of ^{177}Lu-DOTATATE at the time, since the various organs in the human body have different means of transport [20].

Next, we consider the rate of ^{177}Lu-DOTATATE in the nine organs apart from the kidneys and liver. They are stomach, pancreas, adrenal, lung, intestine, femur, spleen, salivary gland, and heart. In each organ, two factors are related to the dynamics, rate of the substance flow into the organs, and transportation rate from organs to the blood system. So, the equations for the concentration of ^{177}Lu-DOTATATE for each organ are shown below.

$$\frac{dSt(t)}{dt} = k_{1,2}Lu(t) - k_{2,1}St(t) \tag{2.4}$$

$$\frac{dP(t)}{dt} = k_{1,3}Lu(t) - k_{3,1}P(t) \tag{2.5}$$

$$\frac{dA(t)}{dt} = k_{1,4}Lu(t) - k_{4,1}A(t) \tag{2.6}$$

$$\frac{dL(t)}{dt} = k_{1,5}Lu(t) - k_{5,1}L(t) \tag{2.7}$$

$$\frac{dI(t)}{dt} = k_{1,6}Lu(t) - k_{6,1}I(t) \tag{2.8}$$

$$\frac{dFe(t)}{dt} = k_{1,8}Lu(t) - k_{8,1}Fe(t) \tag{2.9}$$

$$\frac{dS(t)}{dt} = k_{1,9}Lu(t) - k_{9,1}S(t) \tag{2.10}$$

$$\frac{dSa(t)}{dt} = k_{1,10}Lu(t) - k_{10,1}Sa(t) \tag{2.11}$$

$$\frac{dH(t)}{dt} = k_{1,11}Lu(t) - k_{11,1}H(t) \tag{2.12}$$

There two organs that need to be separately considered are the kidneys and liver since they can eradicate the ^{177}Lu-DOTATATE from the organs. As a result, the additional term about excretion should be added. The model that shows the concentration of ^{177}Lu-DOTATATE in these two organs is represented as the two following equations.

$$\frac{dK(t)}{dt} = k_{1,7}Lu(t) - k_{7,1}K(t) - k_{7,0}K(t) \tag{2.13}$$

$$\frac{dLi(t)}{dt} = k_{1,12}Lu(t) - k_{12,1}Li(t) - k_{12,0}Li(t) \tag{2.14}$$

From equation 2.1 and 2.4 to 2.14, it can be used for both conceptual diagrams. However, the distinction between the two compartments is the transportation of ^{177}Lu-DOTATATE when it moves to the tumor cells. For the first model, Model I, we assume that the substance flow out of the tumor cells will remove from the system. On the other hand, the other model, Model II, has the same flow behavior as the other organs, which is

the ^{177}Lu-DOTATATE will return to the blood system. So, the dynamic of concentration of ^{177}Lu-DOTATATE in the human body in Model II is formed as the equation 2.15.

$$\begin{aligned}\frac{dLu(t)}{dt} =& -k_{1,0}Lu(t) - k_{1,2}Lu(t) - k_{1,3}Lu(t) - k_{1,4}Lu(t) - k_{1,5}Lu(t)\\ &- k_{1,6}Lu(t) - k_{1,7}Lu(t) - k_{1,8}Lu(t) - k_{1,9}Lu(t) - k_{1,10}Lu(t)\\ &- k_{1,11}Lu(t) - k_{1,12}Lu(t) - k_{1,13}Lu(t) + k_{2,1}St(t) + k_{3,1}P(t)\\ &+ k_{4,1}A(t) + k_{5,1}L(t) + k_{6,1}I(t) + k_{7,1}K(t) + k_{8,1}Fe(t)\\ &+ k_{9,1}S(t) + k_{10,1}Sa(t) + k_{11,1}H(t) + k_{12,1}Li(t) + k_{13,1}Tu(t)\end{aligned} \tag{2.15}$$

The kinetic of concentration of ^{177}Lu-DOTATATE in tumors in both situations, Model I and Model II, respectively, can be written as the equation 2.16 and 2.17.

$$\frac{dTu(t)}{dt} = k_{1,13}Lu(t) - k_{13,0}Tu(t) \tag{2.16}$$

$$\frac{dTu(t)}{dt} = k_{1,13}Lu(t) - k_{13,1}Tu(t) \tag{2.17}$$

Therefore, we get the systems of ordinary differential equations to represent both Model I and Model II. The system for Model I is composed of the equation 2.1, 2.4 to 2.14 and 2.16, while the system of Model II contains the equation 2.4 to 2.15 and 2.17.

2.3. Simulation and generating parameters

To solve the systems of the ordinary differential equation, the method of fourth-order Runge-Kutta is selected since this numerical method gives accurate results and small errors when compared with the analytical solution [30–32].

Next, the initial data for the simulation refers to the mice experiment [24]. In the beginning, all organs and tumors do not contain any ^{177}Lu-DOTATATE. Hence, its concentration in each organ is equal to zero, while the initial concentration of ^{177}Lu-DOTATATE depends on the amount of activity prepared for the specific patients. From the referred data, we set $Lu(0) = 71.87322$ %IA/g. The obtained values are calculated from the half-life formula [29], based on ^{177}Lu-DOTATATE at 4 hours of each organ from G. P. Nicolas research and calculating the amount of substance at the beginning time.

We need to find the value of parameters. Since there is a lack of experimental data on the transportation of ^{177}Lu-DOTATATE, we use the stochastic process to estimate the optimal each parameter. The parameters are assumed to be 0.0001, then adding them by 0.0001 per each step. This process aims to find less error of the solution than the experimental data of a radiopharmaceutical used in mice [24]. The parameters related to the flow-in of the ^{177}Lu-DOTATATE are the priority of the consideration. Then we move to the flow out to the blood system and excretion, respectively. The overall process of simulation is shown in Figure 3, and the parameter value for Model I and Model II are shown in Table 2. After that, we use Root Mean Square Error (RMSE) and correlation to determine these models' performance compared with the experimental data, which will discuss in the next section.

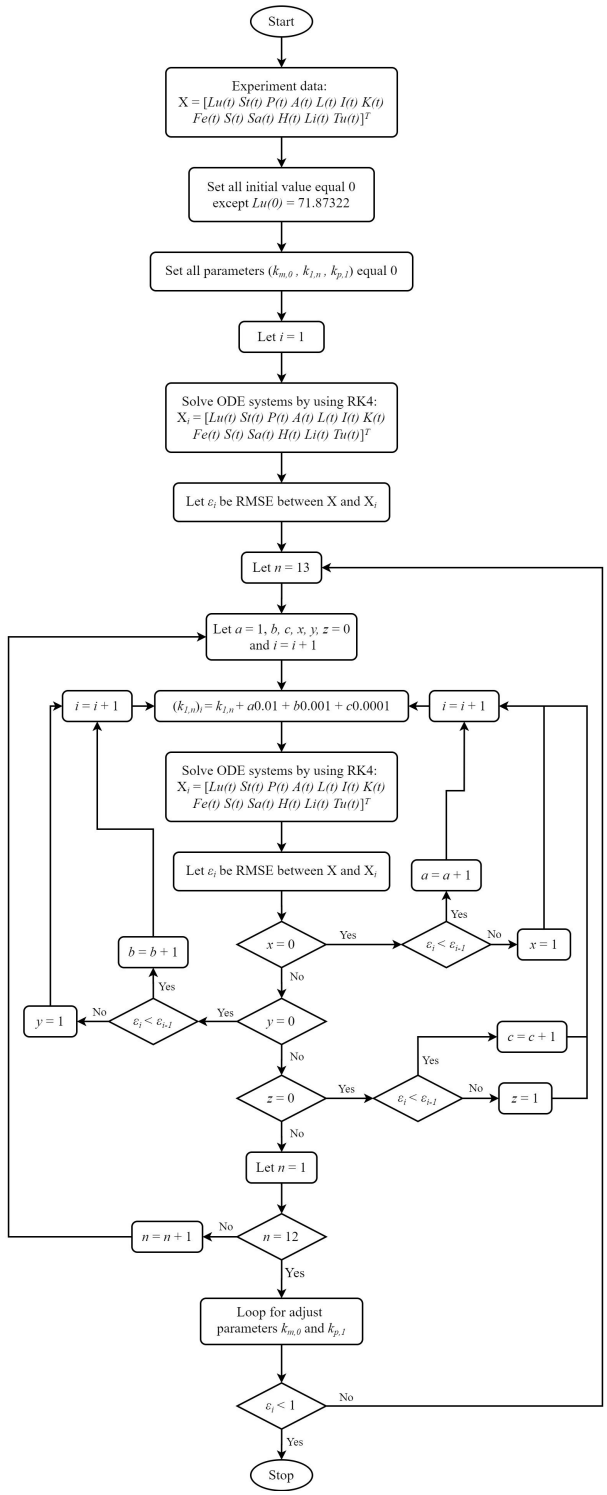


FIGURE 3. The flowchart of the simulation process.

TABLE 2. The parameters and their value for Model I and Model II.

Parameter Model I	Types of parameter	Value (1/hr)	Parameter Model II	Types of parameter	Value (1/hr)
$k_{1,2}$	Flow-in	0.1700	$k_{1,2}$	Flow-in	0.5000
$k_{1,3}$	Flow-in	0.1600	$k_{1,3}$	Flow-in	0.6500
$k_{1,4}$	Flow-in	0.1200	$k_{1,4}$	Flow-in	0.3500
$k_{1,5}$	Flow-in	0.0850	$k_{1,5}$	Flow-in	0.1900
$k_{1,6}$	Flow-in	0.0770	$k_{1,6}$	Flow-in	0.1900
$k_{1,7}$	Flow-in	0.0680	$k_{1,7}$	Flow-in	0.1800
$k_{1,8}$	Flow-in	0.0200	$k_{1,8}$	Flow-in	0.0400
$k_{1,9}$	Flow-in	0.0100	$k_{1,9}$	Flow-in	0.0200
$k_{1,10}$	Flow-in	0.0090	$k_{1,10}$	Flow-in	0.0190
$k_{1,11}$	Flow-in	0.0033	$k_{1,11}$	Flow-in	0.0070
$k_{1,12}$	Flow-in	0.0032	$k_{1,12}$	Flow-in	0.0050
$k_{1,13}$	Flow-in	0.2500	$k_{1,13}$	Flow-in	1.0000
$k_{2,1}$	Flow-out	0.0540	$k_{2,1}$	Flow-out	0.2000
$k_{3,1}$	Flow-out	0.1000	$k_{3,1}$	Flow-out	0.3500
$k_{4,1}$	Flow-out	0.0500	$k_{4,1}$	Flow-out	0.1600
$k_{5,1}$	Flow-out	0.0450	$k_{5,1}$	Flow-out	0.1200
$k_{6,1}$	Flow-out	0.0550	$k_{6,1}$	Flow-out	0.1500
$k_{7,1}$	Flow-out	0.0090	$k_{7,1}$	Flow-out	0.0500
$k_{8,1}$	Flow-out	0.0400	$k_{8,1}$	Flow-out	0.0900
$k_{9,1}$	Flow-out	0.0500	$k_{9,1}$	Flow-out	0.1000
$k_{10,1}$	Flow-out	0.0900	$k_{10,1}$	Flow-out	0.1300
$k_{11,1}$	Flow-out	0.0510	$k_{11,1}$	Flow-out	0.1000
$k_{12,1}$	Flow-out	0.0400	$k_{12,1}$	Flow-out	0.0010
$k_{1,0}$	Excretion	0.0001	$k_{13,1}$	Flow-out	0.3000
$k_{7,10}$	Excretion	0.0550	$k_{1,0}$	Excretion	0.1000
$k_{12,0}$	Excretion	0.0010	$k_{7,0}$	Excretion	0.1300
$k_{13,0}$	Excretion	0.0650	$k_{12,0}$	Excretion	0.0900

3. Results

The simulation starts with the assumption that the NETs patients were injected with ^{177}Lu-DOTATATE, $Lu(0) = 71.87322$ %IA/g, into the vein blood system. We investigate the concentration of ^{177}Lu-DOTATATE from the beginning to 168 hours. The dynamic of concentration of ^{177}Lu-DOTATATE in tumors from Model I and Model II is shown in Figure 4.

From the result, the radiopharmaceutical rapidly moves to the tumors. The concentrations of substance reach at the peak at 16%IA/g and 18%IA/g in Model I and Model II, respectively. After that, the concentrations of substance decrease dramatically. Figure 4 shows that ^{177}Lu-DOTATATE in Model II drops faster than the Model I in the first fifty hours. After fifty hours, the Model II is greater than the Model I. At one hundred hours, the concentration in Model II is higher than Model I, just around 2%IA/g. The trend still is the same until the concentration in Model I is completely zero at 250 hours, while the concentration in Model II vanishes within 300 hours. The dynamic of the concentration in other organs have the same trend with a tumor, which sharply rises in the first ten hours and exponentially decreases and ^{177}Lu-DOTATATE is completely removed from the system.

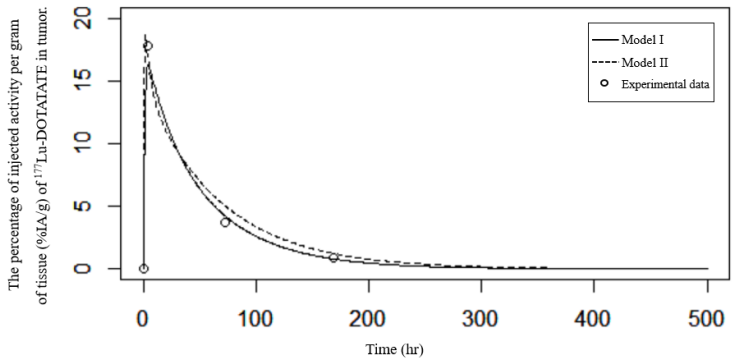


Figure 4. The percentage of injected activity per gram of tissue (%IA/g)of ^{177}Lu-DOTATATE in the tumor from Model I and Model II, where a dot is the experimental data from mice [24].

Next, we consider the simulation results in the kidneys and liver since there is possible toxicity occurring in these organs in the case of exceeding receiving. The results show that the transportation pattern of ^{177}Lu-DOTATATE from the source to the kidneys and liver is almost the same as the tumor.

In kidneys, the amount of radiopharmaceutical significantly rises in the first four hours and hits a peak at just over and nearly 4%IA/g for Model I and Modell II, respectively. Although the maximum concentration of ^{177}Lu-DOTATATE in Model I is higher than the other, its pattern decreases with a rapid rate, and it completely vanishes when the time passed around 200 hours, while Model II spent around 300 hours for complete excretion. The simulation in the kidneys is shown in Figure 5.

There was a small amount of ^{177}Lu-DOTATATE in the liver. The highest concentration of the substance is accounted for around 0.2%IA/g in both Model and Model II, while the Model I gives a higher value. After reaching the peak, the concentration slightly decreases. From 4 to 72 hours after injection, Model II gives a slower drop. However, both models decrease with the same rate at 100 hours and vanish after 200 hours. The dynamic of ^{177}Lu-DOTATATE concentration in the liver is shown in Figure 6.

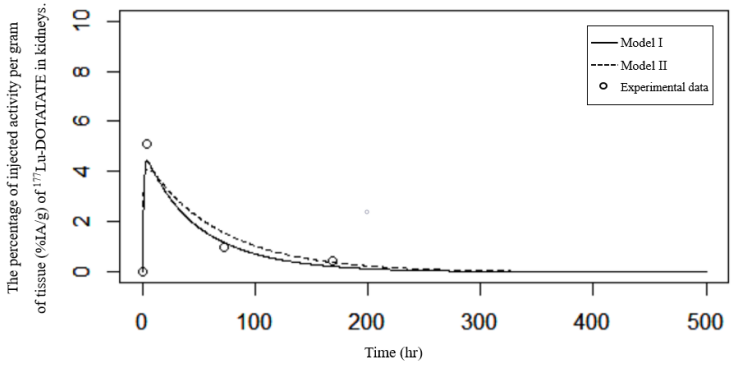


FIGURE 5. The percentage of injected activity per gram of tissue (%IA/g)of ^{177}Lu-DOTATATE in the kidneys from Model I and Model II,where a dot is the experimental data from mice [24].

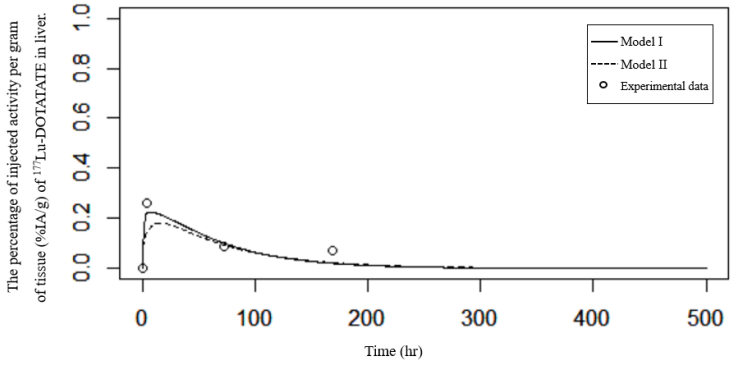


FIGURE 6. The percentage of injected activity per gram of tissue (%IA/g)of ^{177}Lu-DOTATATE in the liver from Model I and Model II,where a dot is the experimental data from mice [24].

We consider the concentration in the overall in Model I and Model II, shown in Figure 7 and Figure 8, respectively. Obviously, a large number of radiopharmaceutical transports to targeted cancer cells at 4-hour past, which just over 16 %IA/g of the initial dose

in Model I and II, respectively. The other substances flow to various organs, such as the stomach, pancreas, adrenal, liver, intestine, and kidneys. The accumulation of the concentration of ^{177}Lu-DOTATATE that flows to the previous organs is just under 60% of the initial dose, while the around 10% left moves to the other parts, such as the femur, spleen, salivary gland, heart, and lungs. The sequence of organs ordered from the highest to lowest concentration is tumors, stomach, pancreas, adrenal, lung, intestine, kidneys, femur, spleen, salivary gland, heart, and liver

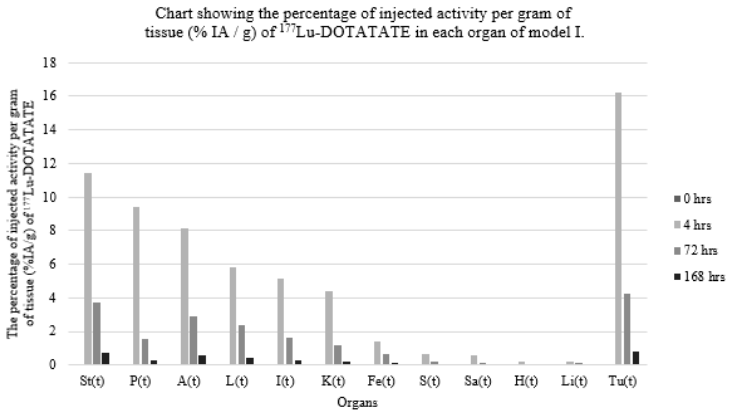


FIGURE 7. The percentage of injected activity per gram of tissue (%IA/g)of ^{177}Lu-DOTATATE in each organ of Model I.

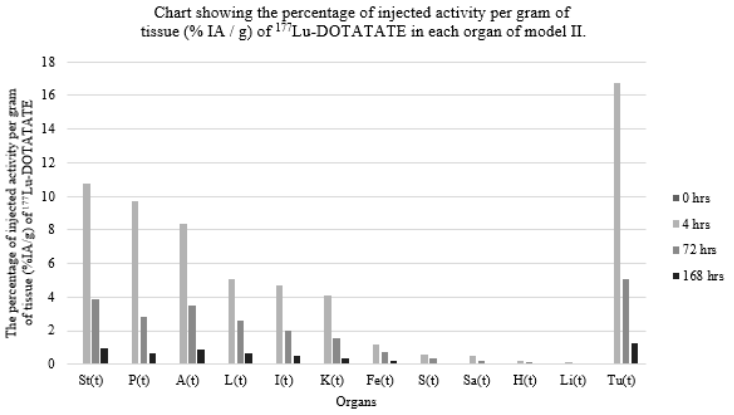


FIGURE 8. The percentage of injected activity per gram of tissue (%IA/g)of ^{177}Lu-DOTATATE in each organ of Model II.

After 72 hours, there are dramatic drops in the concentration in tumors, from around 17%IA/g to 4%IA/g and 5%IA/g for Model I and Model II, respectively. Similarly, this reduction pattern also happens to the change in the organs, which are part of the

digestive system, stomach, pancreas, adrenal, liver, intestine, and kidneys. For the other organs, since they contain a small amount of substance at the beginning, the decreases in concentration are less noticeable.

This reduction still occurs when the time past to 168 hours. Only 1%IA/g left in the tumors, while the other organs have less than 1%IA/g in them, but the substance does not completely disappear from the organs. Both models have nearly the same outcomes. However, in Model II, the concentration of ^{177}Lu-DOTATATE in tumors is slightly higher than Model I since the substance can return to the blood vessel. Overall, the decrease in each time point has the same pattern, except for the pancreas. This organ has a rapid drop at 72 and 168 hours, which means ^{177}Lu-DOTATATE is released faster in the pancreas than the others.

The results of these models were considered the percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE in mice. As of currently, there is no public data on the use of ^{177}Lu-DOTATATE in patients. Therefore, using data from experimental animals is a good alternative to guide the development of a suitable model. The percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE in mice converted human dose based on the equation 2.3 by converting from mice to adult human where $\%IA/g_{mice}$ is the value obtained from the model and replaces M_{mice}, m, and M as 0.0202 kg, 299 g, 60 kg, respectively[24, 33]. Then it yielded the percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE in human kidneys compared to that of mice. As in Figure 9.

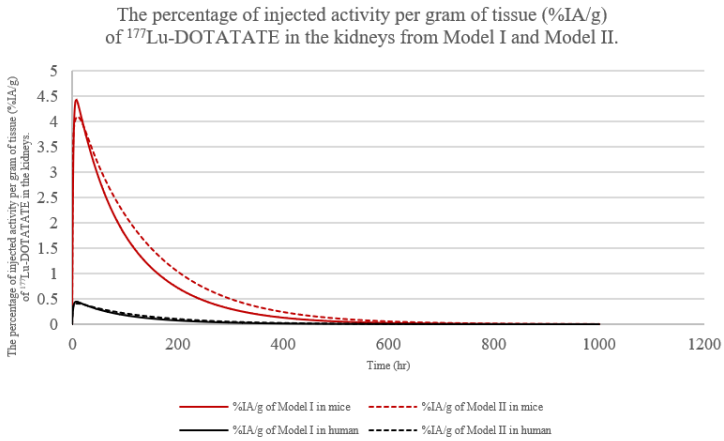


FIGURE 9. The percentage of injected activity per gram of tissue (%IA/g)of ^{177}Lu-DOTATATE in kidneys of Model I and Model II.

Considering the tendency of the percentage of injected activity per gram of tissue (% IA / g) of ^{177}Lu-DOTATATE in mice compared to humans, it is found that there is the same pattern of alteration in mice and humans. It gradually increases and hits the peak, then decreases and level off when the substance is eliminated. However, the amount of substance in the human converted to human content is less than that of mice. It is seen from the maximum quantity of ^{177}Lu-DOTATATE in humans and in mice, which are approximately 0.5%IA/g and 4%IA/g, respectively.

4. Discussion

We compare each model's result in the experimental data since there is a lack of real data for ^{177}Lu-DOTATATE. The research on using another radiopharmaceutical, ^{177}Lu-DOTATATE, in mice is used instead [24]. In the experiment [24], the mice were injected the ^{177}Lu-DOTATATE in their blood system and investigate the concentration in various organs in their body by measuring four times, such as the initial dose (at 0 hours), 4 hours, 72 hours, and 168 hours.

We investigate the models' performance by considering their relation between model results and experimental data using correlation. Besides, the Root Mean Square Error (RMSE) is used to measure the differences between data and simulation [34, 35]. Overall, both models give a moderate linear relationship to the laboratory data in mice, which are 0.6835 and 0.6499 for Model I and Model II, respectively.

The RMSE in all organs and tumors of Model I simulation is lower than in Model II, except for adrenal that higher in Model II. Considering on correlation, both models perform a very strong relationship between raw data and simulation runs, since all part in the human body has at least 0.90 of the correlation value. A comparison between the two models of correlation coefficient shows that Model I has a higher value than Model II. It means that Model I provide a stronger relationship than the other model. Similar to RMSE, only adrenal in Model II that has a high value of correlation than Model I. Therefore, according to RMSE and correlation, Model I tend to have a better performance than Model II. The data of both RMSE and correlation are shown in Table 3. However, the overall correlation between both models is nearly the same. It means that the dynamics of ^{177}Lu-DOTATATE in tumors in different assumptions between Model I and Model II give likely transport behaviors in the patients body. However, the models are generated from different assumptions.

From the above data, it shows that although both models are based on different ^{177}Lu-DOTATATE transport characteristics. That is, Model I considers the removal of radiopharmaceuticals from tumors. While the Model II considers the substance can be transported back into the blood system again. However, the correlation analysis results show that both models provide similar correlation values, with 0.6499 for Model I and 0.6835 for Model II. Showing the amount of substance that is excreted from the tumor does not affect the simulation of changes in the concentration of substances in the human body system. Both models are similar in results.

Since there is no experiment on ^{177}Lu-DOTATATE in patients and the data on the treatment results are not very prevalent. Moreover, there are limitations on trials using animals that cannot be collected at all times, and the raw data on the concentration in the human body is lack. To simulate the models, we generate all parameters by using the estimation process and find the suitable parameters that provide the least error and fit with the experimental data in mice. Although there is a different radiopharmaceutical, they have nearly the same properties, which can be used to interpret the mechanisms of the flow in the human body. The results show that both Model I and Model II give a similar trend in the simulation. The percentage of injected activity per gram of tissue (%IA/g) of ^{177}Lu-DOTATATE in each organ increase in the first period after injection. After that, it starts to drop and is excreted from the blood system. The results are compared with the experimental data and validated by RMSE and correlation coefficient. The Model I has a high performance than another due to less value of RMSE and high value of correlation. This means the consideration of ^{177}Lu-DOTATATE excretion from

TABLE 3. Root mean square error and correlation of Model I in each organ

Targeted organs or tumor	Model I		Model II	
	RMSE	Correlation	RMSE	Correlation
Stomach	0.7397	0.9910	0.9061	0.9894
Pancreas	0.5464	0.9965	0.9738	0.9804
Adrenal	0.9653	0.9878	0.7440	0.9884
Lungs	0.4588	0.9990	0.7562	0.9972
Intestine	0.4221	0.9963	0.5977	0.9883
Kidneys	0.3677	0.9947	0.5926	0.9779
Femur	0.1864	0.9643	0.2535	0.9289
Spleen	0.0556	0.9950	0.1075	0.9578
Salivary gland	0.0743	0.9914	0.1368	0.9086
Heart	0.0359	0.9868	0.0526	0.9226
Liver	0.0315	0.9658	0.0624	0.9206
Tumor	0.8349	0.9982	0.8909	0.9954

the tumor is better than returning to the blood system. The result from both models helps reduce toxicity that occurs in the kidneys and liver. However, it cannot be concluded since there is no evidence to support this situation. In addition, adding the experiment data and results of treatment leads to the more efficient result of the models.

The trend of ^{177}Lu-DOTATATE in NETs patient applies to estimate the maximum amount of substance in the tumor and each organ from the graph of each part. For example, the solution obtained from the simulation on the tumor segment was found at 24 hours. The maximum amount of ^{177}Lu-DOTATATE in the tumor was approximately 16 %IA/g. The doctors can use this information together with their diagnosis, whether the ^{177}Lu-DOTATATE dose was sufficient or not. If this is insufficient, clinicians may consider increasing the amount of ^{177}Lu-DOTATATE administered to the patient. However, they should take into account the effect on the patient's kidneys and liver. In addition, the model can provide the maximum dose of ^{177}Lu-DOTATATE for patients without taking them to have toxicity in the kidneys and liver. Hence, it is the part that can consider the maximum amount of substance in each organ and also consider the effect that will occur in the tumor and those organs.

Based on the results obtained from these models compared with the results of the mice. The trend of ^{177}Lu-DOTATATE was primarily identified in the patient. In this study, the results by converting these model results were considered from mice to a human dose of ^{177}Lu-DOTATATE using equation 2.3 and the percentage of injected activity, gram of tissue (% IA / g) of ^{177}Lu-DOTATATE kidneys. According to Maria Larsson's research on the ^{177}Lu-DOTATATE content in both kidneys from real patients, shown in Figure

10 [36]. It can be seen that the trend of change of ^{177}Lu-DOTATATE obtained by the model was somewhat different from that of ^{177}Lu-DOTATATE in the patient's kidney. However, the model's ^{177}Lu-DOTATATE dose shift model with Maria's research goes the same way. Therefore, this model's outcome can be used as a guideline in determining the preliminary variation of ^{177}Lu-DOTATATE in patients. However, if we have more data than the results. From the models, these models will be more effective.

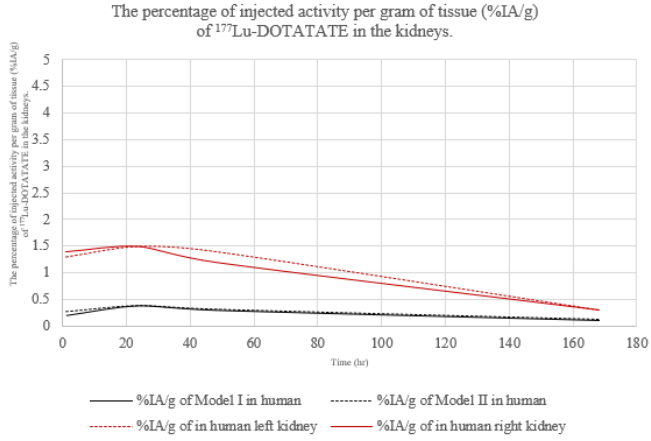


FIGURE 10. The percentage of injected activity per gram of tissue (%IA/g) of ^{177}Lu-DOTATATE in the kidneys from Model I and Model II compare with the data from Maria Larsson's research [36].

Likewise, ^{177}Lu-DOTATATE conversion in other organs from mice to humans was the same as converting ^{177}Lu-DOTATATE in mice kidney to human, which is an important part of model development and parameter estimation. This time to be used as a guide to study the ^{177}Lu-DOTATATE transformation model in patients.

5. Conclusions

Peptide Receptor Radionuclide Therapy plays an important role in the medical treatment for NETs patients. The study on the appropriate use of the ^{177}Lu-DOTATATE which crucial to improve treatment efficiency. In this research, we study the dynamic of the concentration of ^{177}Lu-DOTATATE in NETs patient body by using a mathematical model. The two models are formed under the assumption of the flow of the substance in the human system.

Therefore, the developed mathematical models and estimate parameter can be used to investigate the concentration of ^{177}Lu-DOTATATE in the patient's body in continuous time, considering the maximum of ^{177}Lu-DOTATATE in each organ that may be toxic, such as the kidney and liver. This will help clinicians for planning the appropriate treatment for a specific patient. The dose of ^{177}Lu-DOTATATE can be prepared accurately, which can perform the most efficiency in tumor destruction and does not remain in the body, since the overdose of ^{177}Lu-DOTATATE may cause the side-effect which harmful to patients. Moreover, the simulation results can decrease the number of follow-ups for SPECT/CT examinations, which will help patients save their costs and make more people

access an efficient way for treatment. To improve the model performance, the experiment on using ^{177}Lu-DOTATATE in humans is needed to find the optimal parameters so that we can use validate the models and decrease the value of the error of the model.

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