

UNCERTAINTIES OF ORGAN ABSORBED DOSES TO PATIENTS FROM ^{18}F -CHOLINE

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ABSTRACT

Radiation doses of radiopharmaceuticals to patients in nuclear medicine are, as the standard method, estimated by the administered activity, medical imaging (e.g. PET imaging), compartmental modeling and Monte Carlo simulation of radiation with reference digital human phantoms. However, in each of the contributing terms, individual uncertainty due to measurement techniques, patient variability and computation methods may propagate to the uncertainties of the calculated organ doses to the individual patient. To evaluate the overall uncertainties and the quality assurance of internal absorbed doses, a method was developed within the framework of the MADEIRA Project (Minimizing Activity and Dose with Enhanced Image quality by Radiopharmaceutical Administrations) to quantitatively analyze the uncertainties in each component of the organ absorbed doses after administration of ^{18}F -choline to prostate cancer patients undergoing nuclear medicine diagnostics.

First, on the basis of the organ PET and CT images of the patients as well as blood and urine samples, a model structure of ^{18}F -choline was developed and the uncertainties of the model parameters were determined. Second, the model parameter values were sampled and biokinetic modeling using these sampled parameter values were performed. Third, the uncertainties of the new specific absorbed fraction (SAF) values derived with different phantoms representing individual patients were presented. Finally, the uncertainties of absorbed doses to the patients were calculated by applying the ICRP/ICRU adult male reference computational phantom. In addition to the uncertainty analysis, the sensitivity of the model parameters on the organ PET images and absorbed doses was indicated by coupling the model input and output using regression and partial correlation analysis.

The results showed that the uncertainty factors of absorbed dose to patients are in most cases less than a factor of 2 without taking into account the uncertainties caused by the variability and uncertainty of individual human phantoms. The sensitivity study showed that the metabolic transfer parameter from the blood to soft tissues has a strong influence on blood sample collection from the beginning until 500 min. post administration; the transfer pathways between blood and liver impact strongly the liver imaging during the time course. The results of this study suggest that organ image acquisition of liver and kidneys after 100 min. as well as blood and urine sample collection are necessary for the reduction of uncertainties of absorbed dose estimates to patients.

Keywords: Uncertainty, sensitivity, ^{18}F -choline, PET, model, absorbed dose

1. INTRODUCTION

Risk assessment of radiation exposure in nuclear medicine needs quantitative dose information. The mathematical models and dosimetric models^[1,2] used to calculate the organ absorbed doses to patients are subject to large uncertainties inherent to all steps of the processes including administered activity of radiopharmaceuticals, patient PET image acquisition, biokinetic model building and selection, parameter estimation, image segmentation of patients, development of human mathematical or voxel phantoms, Monte Carlo simulations of radiation transport with phantoms for calculation of the SAF values, and dosimetric approaches for absorbed dose calculations^[3,4]. The risk of an individual patient depends on the individual patient dose; determination of the latter requires knowledge of the anatomy (CT or MRI image set) and knowledge of the radionuclide distribution (SPECT or PET image set) in each individual patient^[5].

To evaluate the overall uncertainties and the quality assurance of internal organ absorbed doses for individual patient, each component of uncertainties in all steps of the chain of the dose calculation procedure needs to be evaluated and analyzed. Specifically, the uncertainty components during the acquisition of the organ images (e.g. PET images) includes

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the system spatial resolution, scatter fraction, counter losses and random measurement and PET system sensitivity (i.e. rate in counts per second that true coincidence events are detected for a given source strength)^[6] and etc; during the model building and model selection, uncertainties caused by model structures and model parameters due to the variability of the patients and measurement uncertainties of images and bioassays may influence the calculated organ doses.

In the framework of the MADEIRA Project (Minimizing Activity and Dose with Enhanced Image quality by Radiopharmaceutical Administrations), a method of uncertainty and sensitivity analysis was developed. This method was applied and designed to find out the main uncertainty sources within the dose calculation procedure, so that hardware and software can be optimized to reduce the radiation doses to the patients. As an example, the developed method was applied to the new compartmental model of ^{18}F -choline^[7]. The influence of metabolic pathways represented as model parameters on the patient organ PET images and the blood and urine sample collections was identified. The uncertainties of absorbed dose to patients were estimated using the ICRP/ICRU adult male reference computational phantom^[8]. Some implications of the information of uncertainties and sensitivities on the reduction of the uncertainties in PET image acquisition and bioassays are discussed.

2. MATERIALS AND METHODS

2.1 The compartmental model and parameters of ^{18}F -choline

Patient measurements were performed at the Nuclear Medicine Department at the Skåne University Hospital Malmö^[9] according to the protocol approved by the Regional Ethical Vetting Board at Lund University. The ^{18}F -choline was synthesized at the synchrotron facilities at Lund University Hospital and delivered to Malmö. Six patients suffering from prostate cancer participated in the present study. The activity concentrations in the liver, kidneys, spleen, and urinary bladder were determined using the implemented software tool provided with the Philips Gemini PET/CT scanner. The blood and urine samples were measured in an automatic gamma counter (WIZARD 1480, Wallace). A correction for the counting efficiency at different activity levels was implemented. The distribution data of the radioactivity in the organs and tissues were used to build the compartmental model of the ^{18}F -choline biokinetics in patients^[7,9] (Figure 1).

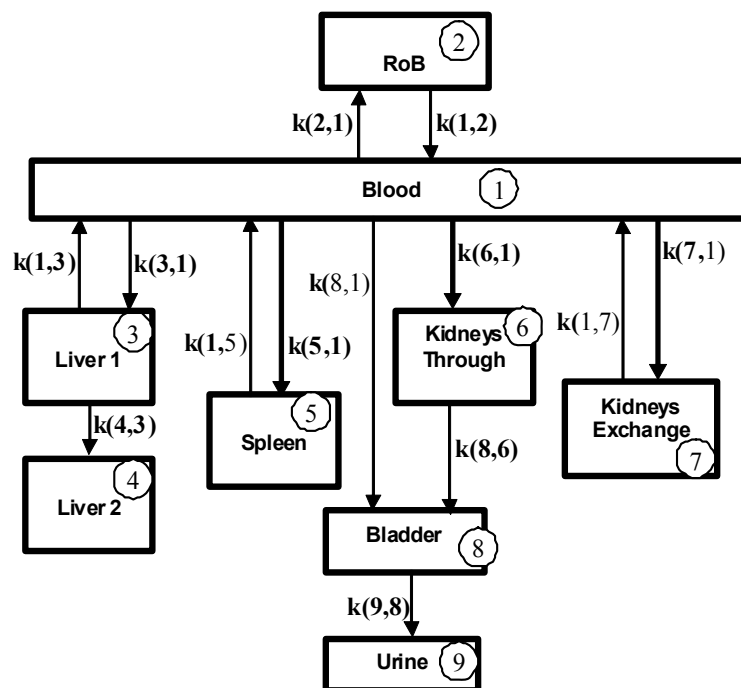


Figure 1: The compartmental model of ^{18}F -choline

The blood is the central exchange compartment, where the injected radiopharmaceutical is initially distributed. Compartments representing liver (divided into liver 1 and 2), kidneys (divided into kidneys through and exchange), spleen and urinary bladder were connected to the central compartment blood. A further compartment (Rest of the Body, RoB) was introduced to account for the material which is transported to further organs and tissues in addition to those explicitly represented in the compartmental model. The transfer rates between compartments are the parameters of the model. In the process of modeling and determination of model parameters, different software packages were used with different optimization and minimization techniques, and differential equation solvers. Additionally, the population kinetic analysis method was introduced to estimate the mean values and the standard deviations (SD) of model parameters for the participated patients^[7].

2.2 Uncertainty and sensitivity analysis

The uncertainty and sensitivity analysis method is widely used in the analysis of complicated mathematical models^[10,11,12]. Uncertainty analysis is the computation of the total uncertainty induced in the output by quantified uncertainty in the inputs and models, and the attributes of the relative importance of the input uncertainties in terms of their contributions, whereas sensitivity analysis is the computation of the effect of changes in input values or assumptions, including boundaries and model functional form, on the outputs^[11]. In the present study, the following steps were included in the analysis.

2.2.1 Uncertainty analysis of model input parameters

The sources of uncertainty of the model parameters were carefully identified and evaluated using various software packages^[7]. The model structure is one uncertainty factor; however this model uncertainty was not analyzed in the present study, because it needs further methods, e.g. model selection methods and Akaike's information criterion. The uncertainties of the model parameters were represented as standard deviation according to the *Guide to the Expression of Uncertainty in Measurement* published by the International Organization for Standardization (ISO)^[13]. The ranges and distributions of model parameters were assigned to a coverage factor of 2.33 and the normal distribution, respectively, on the derived values and SD^[7] analyzed from the experimental measurement results.

2.2.2 Sampling of the input parameter values

Sampling techniques are needed to generate samples of the model input parameters (variables). Generally, random, such as Monte Carlo simulation, or stratified, such as the Latin hypercube sampling (LHS)^[10], sampling techniques are applied. In the present study, the LHS was used because it can improve the efficiency of Monte Carlo simulations by picking the input samples better and sample the entire domain more systematically.

2.2.3 Biokinetic modeling and calculation of time-integrated activity

To predict the retentions of ¹⁸F-choline in the body and organs of patients and the urinary excretion; and to calculate the time-integrated activity^[14] in source organs, biokinetic modeling is required. A computer program^[15] (BIOKINDOS – used for biokinetic modeling and internal dose calculation) was written at the Helmholtz Zentrum München – German Research Center for Environmental Health (HMGU), and several hundreds of computer simulations were performed with the sampled input parameters. A sample size of 500 was chosen in the simulation, so that it is 95 % confident that the actual 97.5th percentile of the model output is between 96th and 99th percentiles^[11].

2.2.4 Organ absorbed dose calculation

The dosimetric models were developed by the International Commission on Radiological Protection (ICRP) and the Medical Internal Radiation Dose (MIRD) Committee for the calculations of patient organ absorbed doses received from radiopharmaceuticals^[1,2,14].

$$D_T = c \sum_S \tilde{A}_S \times \text{SAF}(T \leftarrow S)$$

where $\tilde{A}_S$ is the time-integrated activity in source organ S per unit administered activity; SAF(T←S) is the specific absorbed fraction in target organ T per unit cumulated activity released from the organ S; c is a constant.

The dosimetric models were implemented into the computer program BIOKINDOS, and the organ absorbed doses to patients can be calculated using the sampled values of the model parameters and the SAF values.

2.2.5 Determination of uncertainties of model prediction and patient absorbed doses

Model predictions for different organs and tissues at different time periods resulted in huge amounts of data. For a better presentation of this data, the percentile was used for data reduction and to interpret the uncertainty of the results. For each organ and tissue at a different time point, modeled data are presented as 2.5th, 50th and 97.5th percentiles for comprising the 95 % confidence interval of the results.

2.2.6 Sensitivity analysis of model parameters

In order to identify the most influential parameters in the model, the concepts of the standardized rank regression coefficient (SRRC) and the partial rank correlation coefficient (PRCC)^[10] were applied. The SRRC can be computed by constructing regression models, which approximate the rank transformations of the sampled model input and output variables. The PRCC measures the rank correlation between one defined output variable with an input variable, under the condition that the indirect influence on this defined output variable due to other further input variables is somehow eliminated.

2.3 Monte Carlo simulations of radiation transport with voxel phantoms and specific absorbed fraction

The SAF values were calculated by applying Monte Carlo simulation of radiation transport with human digital phantoms. The phantom used for the dose calculations is the new ICRP/ICRU reference voxel-based adult male computational phantom (Figure 2)^[8]. This phantom is based on medical image data of a real person, and is consistent with the information of ICRP Publication 89^[16] on the reference anatomical parameters for male subjects. The reference voxel phantom was developed at HMGU in collaboration with the ICRP Task Group DOCAI. The phantom consists of nearly 2 million voxels of size $2.137 \times 2.137 \times 8 \text{ mm}^3$ (i.e. 36.54 mm^3). In addition to the reference voxel phantoms, several male voxel phantoms, e.g. Frank, Golem, Visual Human and one real patient voxel phantom developed at HMGU^[17] and the Voxelman phantom developed by Zubal et al.^[18] were used for Monte Carlo simulations. By doing so, the uncertainty and variability of SAFs can be evaluated.

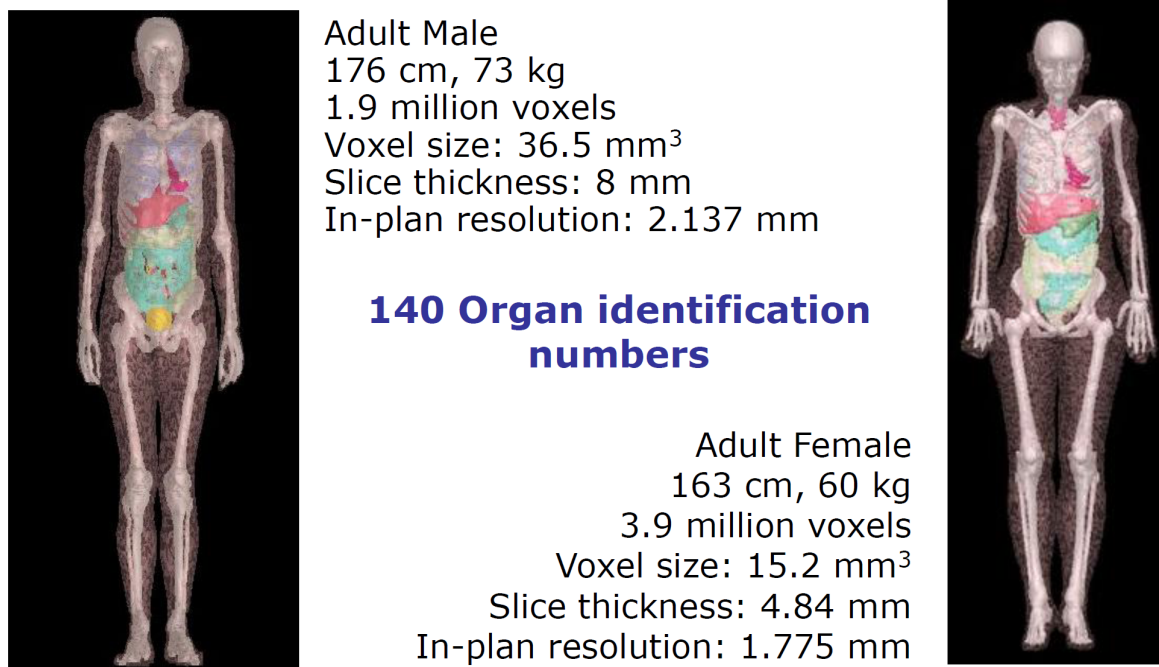


Figure 2: ICRP/ICRU adult female and male reference computational phantoms

Calculations of SAF values were performed with the EGSnrc code package^[19] for photons and electrons. All relevant source regions, more than 65 target regions, and photon and electron energies from 10 keV to 10 MeV were considered

and simulated. The cut-off energies were 2 keV for photons and 20 keV for electrons^[20]. Since the skeletal target tissues – endosteum and red bone marrow (RBM) – could not be represented on voxel basis in the reference computational phantoms, some approximations had to be applied, which are described in detail by Zankl et al.^[20]

3. RESULTS AND DISCUSSION

3.1 Uncertainties of model parameters

The uncertainties of the model parameters are listed in Table 1. The 98% confidence intervals (CI) of the input parameter values were calculated by adding and subtracting 2.33 times the values of the standard deviation, to and from the mean value. The transfer rate from bladder to urine was assumed to follow a triangular distribution and the mean value is determined according to the 60 min. voiding interval time of the patients.

Table 1: Parameter values (min^{-1}) of transfer rates derived from the measured PET imaging, blood and urine samples

Parameter		Mean	SD	98% CI		Distribution
Blood → Liver1	k(3,1)	1.83E-02	2.72E-03	1.20E-02	2.46E-02	Normal
Liver1 → Blood	k(1,3)	2.56E-02	5.54E-03	1.27E-02	3.85E-02	Normal
Liver1 → Liver2	k(4,3)	1.54E-02	6.37E-03	5.58E-04	3.02E-02	Normal
Blood → Spleen	k(5,1)	1.18E-03	4.92E-04	3.36E-05	2.33E-03	Normal
Spleen → Blood	k(1,5)	8.73E-03	3.56E-03	4.35E-04	1.70E-02	Normal
Blood → Bladder	k(8,1)	2.64E-03	9.79E-04	3.59E-04	4.92E-03	Normal
Blood → Kidneys Exchange	k(7,1)	1.66E-02	5.45E-03	3.90E-03	2.93E-02	Normal
Kidneys Exchange → Blood	k(1,7)	1.91E-01	6.29E-02	4.44E-02	3.38E-01	Normal
Blood → Kidneys Through	k(6,1)	2.90E-03	5.29E-04	1.67E-03	4.13E-03	Normal
Kidneys Through → Bladder	k(8,6)	3.45E-03	1.42E-03	1.41E-04	6.76E-03	Normal
Blood → RoB	k(2,1)	5.51E-02	4.54E-03	4.45E-02	6.57E-02	Normal
RoB → Blood	k(1,2)	4.49E-03	1.40E-03	1.23E-03	7.75E-03	Normal
Bladder → Urine	k(9,8)	-	8.33E-03	2.08E-02	2.08E-02	Triangular
Volume (ml)		1.27E+04	4.40E+03	2.35E+03	2.30E+04	Normal

3.2 Uncertainties of model predictions

The uncertainties of the model predictions are shown in Figure 3, for comparison purpose, the activities in blood samples measured by an automatic gamma counter and the activity concentrations evaluated from PET images are also presented. The uncertainty of the model prediction can be quantitatively expressed by the uncertainty factor (UF) which is defined by the maximum of B/A and C/B assuming that A stands for the value at the 2.5th percentile (lower value), B for the 50th percentile (median value) and C for the 97.5th percentile (upper value).

In the time course from 1 min. to 500 min., the UF of activities in the liver ranged from 1.2 to 2.1; the UF of activities in the spleen ranged from 1.6 to 3.0; the UF of activities in the kidneys ranged from 1.4 to 1.9; and the UF of the plasma clearance ranged from 1.7 to 4.5. The results showed that a high uncertainty was found in the spleen and a comparative smaller uncertainty in the liver and in the kidneys. However, the UF of the activity concentration in the plasma is high due to a high uncertainty of plasma volume. Because in the collection of the blood sample, only blood samples from few patients were taken in the first minute, and the blood sample from most patients were firstly taken after 30 minutes.

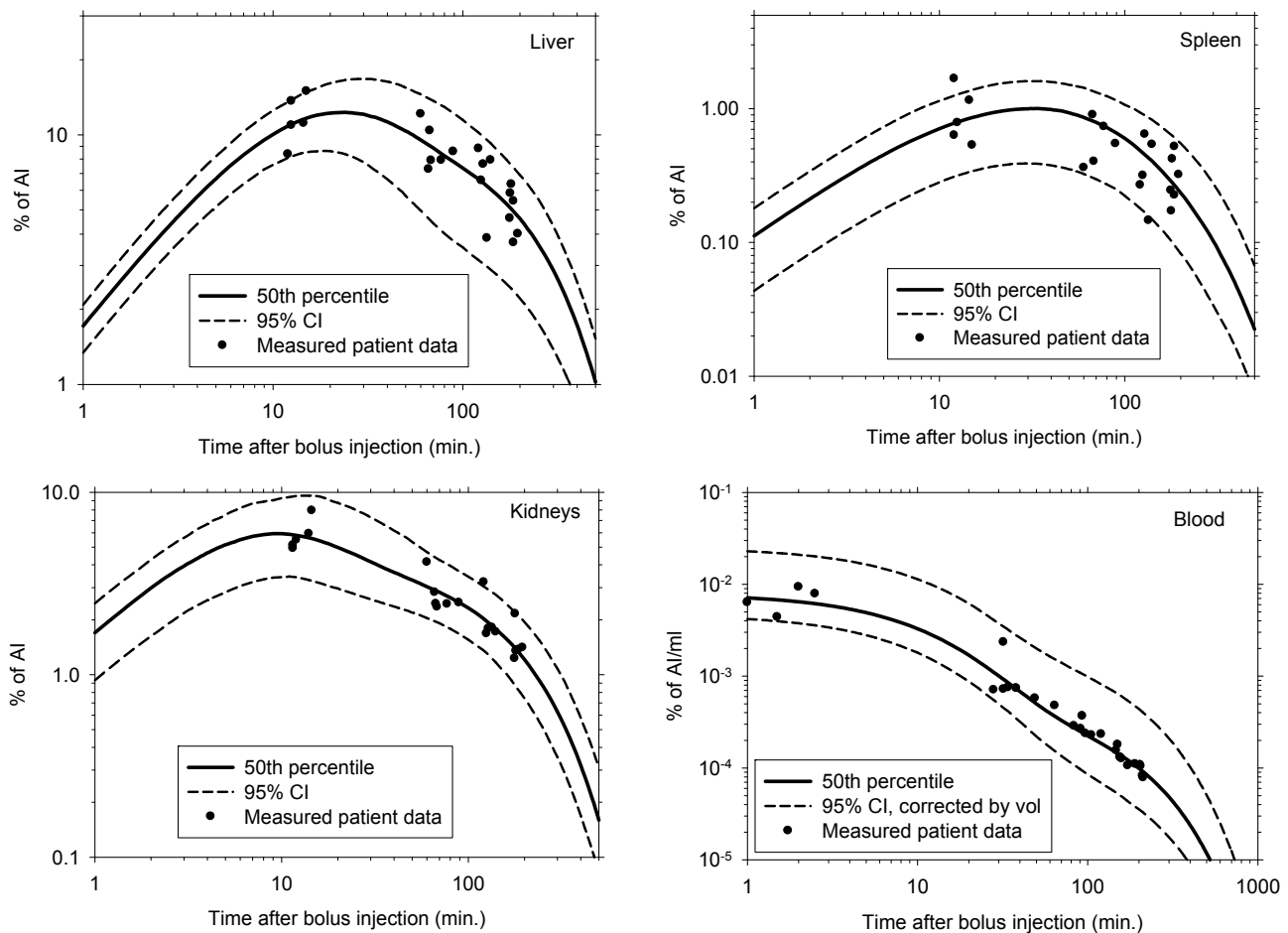


Figure 3: Uncertainties of blood clearance and organ retention of ^{18}F -choline predicted by the compartmental model and comparison to the patient PET images and blood sample

3.3 Uncertainties and variability of SAFs for different voxel phantoms

The SAFs calculated with different voxel phantoms showed a large uncertainty and variability. As an example, the SAF(UB-wall <-UB-cont) and SAF(R-marrow<-T-body) were presented in Figure 4. The SAF values of the Reference Male were taken as the mean value and the concept of the uncertainty factor (UF) was applied. It is assumed that the upper and lower values were the SAF values of the MalPat1 and the Voxelman phantoms, respectively, for the UB-cont as source organ, and the upper and lower values were the SAF values of the Voxelman and the Visible Human phantoms, respectively, for T-body as source organ.

For UB-cont as source organ, the UF of SAF(UB-wall <-UB-cont) for photons ranged from 1.7 to 5.5 for the energy range considered (from 10 keV to 10 MeV). The UF showed a high value of 5.5 in the lower energy range, e.g. 15 keV. At the energy of 511 keV (i.e. the annihilation photon energy), the UF of the same SAF was about 3.1. For electrons, the UF of this SAF ranged from 2.3 to 6.0 for the entire energy range studied (10 keV to 10 MeV); at the energy of 250 keV, the average electron energy released by ^{18}F , the UF of the SAF is about 5.3. The higher UF of SAF(UB-wall <-UB-cont) were found in a patient voxel phantom (MalPat1) for both photons and electrons, the lower UF of the SAFs in the Voxelman phantom.

Taking the total body as the source organ, The UF of the SAF(R-marrow<-T-body) ranged from 1.1 to 3.1 for photons and from 1.1 to 2.1 for electrons in the entire energy range (10 keV to 10 MeV).

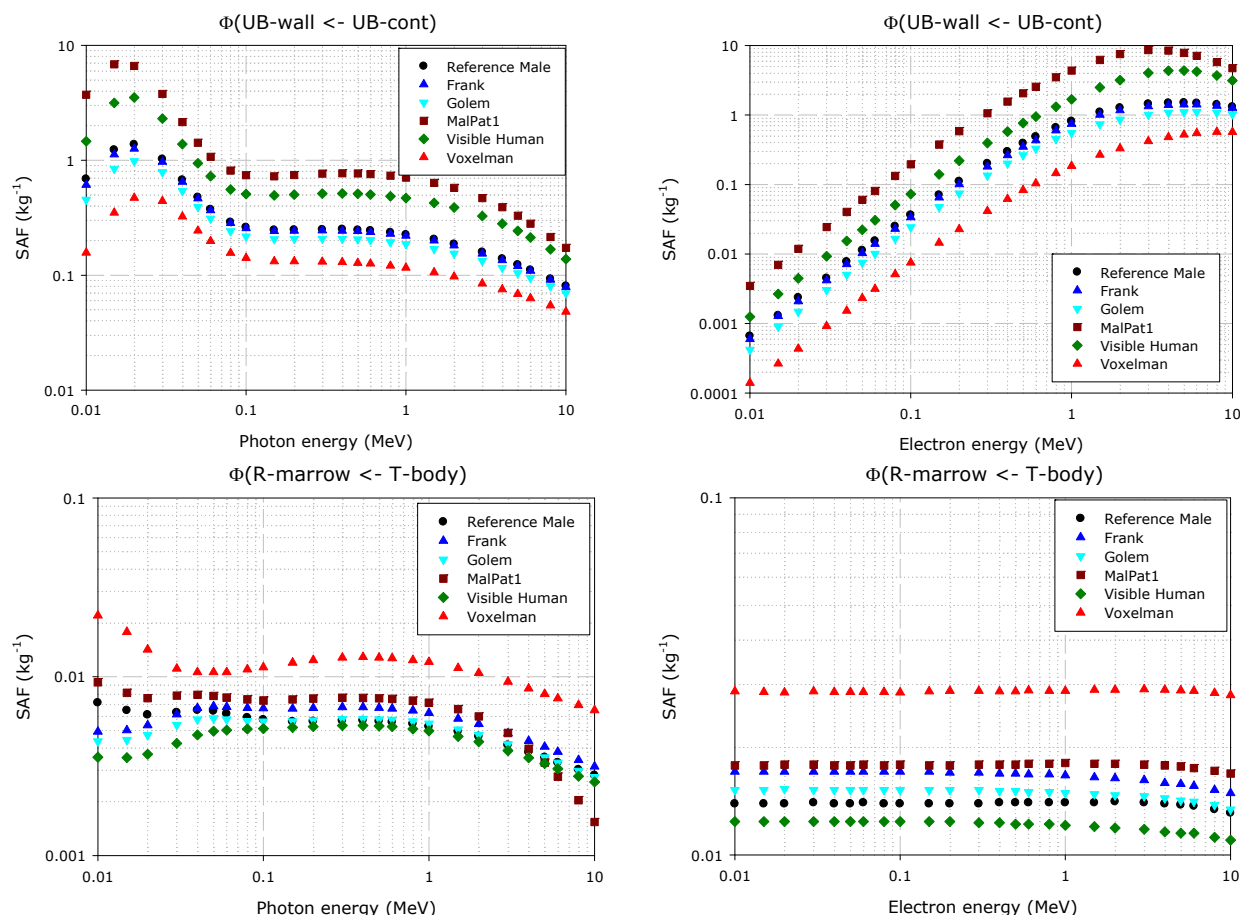


Figure 4: Uncertainties and variability of SAFs calculated with different male voxel phantoms. UB-wall: urinary bladder wall; UB-cont: urinary bladder content; R-marrow: red marrow; T-body: total body

3.4 Sensitivities of model parameters

Various model parameter sensitivities are shown in Figure 5. The metabolic pathway from blood to soft tissues shows a strong influence on the activity in the blood immediately after the radiopharmaceutical administration until 500 min. later. The metabolic pathways from liver to blood and from blood to liver influence the radiopharmaceutical concentration in the liver strongly during the time course, especially in the first 100 minutes (see Figure 5 for Liver 1). After 100 minutes, the transfer pathways from RoB to blood and from liver 1 to liver 2 begin to influence the retention in liver strongly. The transfer pathways between the blood and kidneys impact the retention in kidneys from the first minute until 500 minutes (see Figure 5 for Kidney Exchange). The sensitivity results of liver and kidneys imply that the PET images of liver and kidneys until 100 minutes are important for the estimation of the model parameters and the reduction of uncertainty of model predictions in these organs. For the urine samples, the metabolic pathway from blood to bladder has the largest influence; after 100 min., the transfer pathway from bladder to urine becomes much more influential on the concentration in the urine.

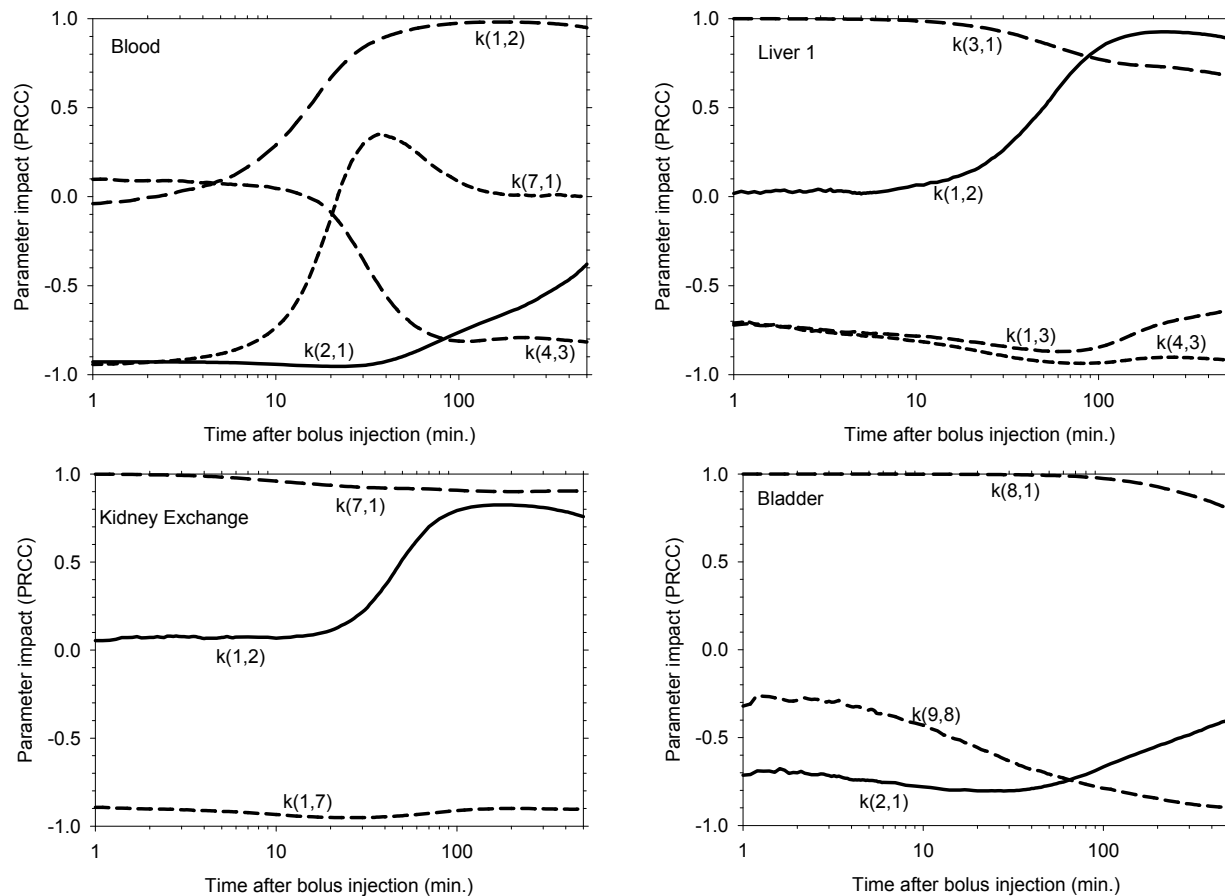


Figure 5: Model parameter sensitivity (indicated as PRCC) of the blood clearance of ^{18}F -choline, and the ^{18}F -choline retention in the liver, the kidneys and the urine in the bladder

3.5 Uncertainties of absorbed organ doses

The uncertainty factors of absorbed doses to patients are in most cases less than a factor of 2, where the highest value of 2 was found for the ‘other tissues’, and the lowest value for the bladder wall (Table 2). The UF of 2 is close to the value found in earlier studies for other radiopharmaceuticals^[3,21]. However, the uncertainties contributed from the variability of individual voxel SAFs are not included in the present study and will be examined extensively in a future study. The two main factors influencing the organ absorbed doses are the self-irradiation and the time-integrated activities in the source organs (Table 3).

Table 2: Uncertainties of organ absorbed doses of ^{18}F -choline to patients

Organ	Dose coefficients (mGy/MBq)		
	Percentile		
	50th	2.5th	97.5th
Liver	0.069	0.05	0.088
Kidneys	0.094	0.068	0.12
Spleen	0.046	0.025	0.067
Bladder wall	0.027	0.02	0.034
Other tissues	0.02	0.01	0.03

Table 3: Impact (indicated as PRCC) of time-integrated activities in source organ on absorbed doses in target organs

Source organ	Target organ				
	Bladder	Kidneys	Liver	Spleen	Other
UB-cont*	1.0				
Kidneys		1.0		0.5	0.8
Liver			1.0		
Spleen				1.0	0.6
Blood				0.7	
Other					0.6

*UB-cont: Urinary bladder contents

In the present study, a detailed compartmental model was established to describe the organ and the blood activities, and urinary excretion on the basis of PET image acquisitions and the pharmaceuticals compound in the blood and urine. This analysis procedure is not always performed in practice of nuclear medicine, there in most cases, only single organ activity is analyzed and dose coefficients recommended by the ICRP are used. However, the determination of absolute radioactivity requires definition of regions of interests (ROIs) corresponding to the source regions as differentiated from their adjacent or surrounding background activity^[4]. The uncertainty might be large in these processes of quantification of organ activity and measurement of blood and urinary samples. The methods developed in the present work can be applied to identify the uncertainty component in different steps of estimation of organ absorbed doses to patients, so that technical improvements might be applied to reduce the uncertainties in the identified main steps. In addition, this analysis method provides more reliable and confidence interval of dose coefficients which can be used in nuclear medicine practice.

4. CONCLUSIONS

In the framework of the MADEIRA Project, a method for uncertainty analysis of organ absorbed doses to patients in nuclear medicine diagnostics was developed. This method was applied to the uncertainty analysis of organ absorbed doses to prostate cancer patients administered by the radiopharmaceutical ¹⁸F-choline. It was found that the metabolic transfer pathway from the blood to the rest of body has the largest influence on the radiopharmaceutical concentration in the patient blood samples. For the absorbed doses in liver and kidneys, the parameters characterizing the metabolic transfers between blood and the liver and kidney compartments have the largest influence. We suggest that organ image acquisition of liver and kidneys until 100 min., and blood and urine sample collections are necessary for the reduction of uncertainties of absorbed dose estimates to patients.

The uncertainty factors of absorbed doses to patients are in most cases less than a factor of 2 when the uncertainties caused by the variability of individual human phantoms are not taken into account. The preliminary results of the SAF values derived from different voxel phantoms, which might represent different patients, showed large uncertainties at the beta average energy of 250 keV and the annihilation photon energy of 511 keV. The influence of uncertainties of SAF values on absorbed dose might be large and is under investigation. The appropriate methods, e.g. variance decomposition may be applied to quantitatively determine and distinguish the contributions of the two main uncertainty sources, i.e. the model parameters and the SAF values. Thus, a practical statistical framework will be set up to identify the most important factors in the chain from image acquisition and bioassay collections to the estimation of organ absorbed doses to patients in nuclear medicine diagnostics.

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REFERENCES

1. ICRP. Radiation dose to patients from radiopharmaceuticals. ICRP Publication 53. Ann. ICRP 18(1-4) (1987).
2. Loevinger, R., Berman, M. A revised schema for calculating the absorbed dose from biologically distributed radionuclides. MIRD pamphlet no. 1, revised (New York: Society of Nuclear Medicine) (1976).
3. Stabin, M. G. Uncertainties in internal dose calculations for radiopharmaceuticals. J. Nucl. Med. 49: 853-860 (2008).
4. Siegel, J. A. et al. MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. J. Nucl. Med. 40: 37S-61S (1999).
5. ICRU. Absorbed-dose specification in nuclear medicine, ICRU Report 67. (2002).
6. NEMA. Performance measurements of positron emission tomographs. NEMA Standard Publication NU 2-2007. (Rosslyn, VA: National Electrical Manufacturers Association) (2007).
7. Janzen, T., et al. Compartmental model of ^{18}F -choline. Proc. of SPIE Vol. 7626: 76261E1-E9 (2010).
8. ICRP. Adult reference computational phantoms. ICRP Publication 110. Ann. ICRP 39(2) (2009).
9. Uusijärvi, H., Nilsson, L.-E., Bjartell, A. and Mattsson A. Biokinetics of ^{18}F -choline studied in four prostate cancer patients. Radiat. Prot. Dosim. 139: 240-244 (2010).
10. Iman, R. L. and Conover, W. J. Sensitivity analysis techniques: self-teaching curriculum. NUREG/CR-2350, SAND81-1978. (Albuquerque: Sandia National Laboratories) (1982).
11. Morgan, M.G. and Henrion, M. Uncertainty: A guide to dealing with uncertainty in quantitative risk and policy analysis (New York: Cambridge University Press) (1990).
12. Saltelli, A., et al. Global sensitivity analysis. The primer (Chichester: John Wiley & Sons Ltd.) (2008).
13. ISO. Guide to the expression of uncertainty in measurement (GUM). 1st ed., corrected and reprinted version (Geneva: International Organization for Standardization) (1995).
14. Bolch, W. E., Eckerman, K. F., Sgouros, G. and Thomas, S. R. MIRD pamphlet no. 21: A generalized schema for radiopharmaceutical dosimetry—standardization of nomenclature. J. Nucl. Med. 50: 477-484 (2009).
15. Li, W.B. and Hoeschen, C. Uncertainty and sensitivity analysis of biokinetic models for radiopharmaceuticals used in nuclear medicine. Radiat. Prot. Dosim. 139: 228-231 (2010).
16. ICRP. Basic anatomical and physiological data for use in radiological protection: reference values. ICRP Publication 89. Ann. ICRP 32(3-4) (2002).
17. Petoussi-Henss, N., Zank, M., Fill, U. and Regulla, D. The GSF family of voxel phantoms. Phys. Med. Biol. 47(1):89-106 (2002).
18. Zubal, I.G., Harrell, C.R., Smith, E.O., Rattner, Z., Gindi, G. and Hoffer, P.B. Computerized 3-Dimensional segmented human anatomy. Med. Phys. 21(2): 299-302 (1994).
19. Kawrakow, I. and Rogers, D.W.O. The EGSnrc code system: Monte Carlo simulation of electron and photon transport. Technical Report PIRS-701. (Ottawa: National Research Council of Canada (NRCC)) (2003).
20. Zankl, M., Petoussi-Henss, N., Janzen, T., Uusijärvi, H., Schlattl, H., Li, W.B., Giussani, A. and Hoeschen, C. New calculations for internal dosimetry of beta-emitting radiopharmaceuticals. Radiat. Prot. Dosim. 139(1-3): 245-249 (2010).
21. Roedler, H.D. Accuracy of internal dose calculations with special consideration of radiopharmaceutical kinetics. In: Watson, E.E., Schlafke-Stelson, A., Coffey, J.L., Cloutier, R.J., eds. Third International Radiopharmaceutical Dosimetry Symposium, Proceedings of a Conference held at Oak Ridge, Tennessee, 1980. HHS Publication FDA 81-8166. (Rockville, MD: Department of Health and Human Services, Bureau of Radiological Health.): 1-20 (1981).