

ORIGINAL ARTICLE

Accurate radiation dosimetry of [⁶⁴Cu]Cu-DOTATOC using the Monte Carlo simulation

Milad Peer-Firozjaei¹, Nasim Vahidfar², Mohsen Bakhshi Kashi², Peyman Sheikhzadeh^{2,3,4}

¹Student Research Committee, Babol University of Medical Sciences, Babol, Iran

²Department of Nuclear Medicine, Imam Khomeini Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

³Department of Biomedical Physics and Engineering, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁴Research Center for Nuclear Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author:

Dr. Peyman Sheikhzadeh

Address: Department of Nuclear Medicine, Imam Khomeini Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Email: sheikhzadeh-p@sina.tums.ac.ir

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ABSTRACT

Introduction: Copper-64 labeled DOTATOC ([⁶⁴Cu]Cu-DOTATOC) is an emerging theranostic agent for neuroendocrine tumors (NETs), offering both high-resolution PET imaging and therapeutic potential. Accurate patient-specific dosimetry is critical to balance diagnostic benefits with radiation safety. This study aimed to perform voxel-based internal dosimetry of [⁶⁴Cu]Cu-DOTATOC using Monte Carlo simulations, enabling precise three-dimensional absorbed dose estimation in normal organs and tumor nodules.

Methods: PET/CT images from patient imaged at two time points post-injection of [⁶⁴Cu]Cu-DOTATOC were analyzed. Anatomical segmentation was performed, and time–activity curves were fitted with bi-exponential models. GATE v8.1 Monte Carlo simulations incorporating the full ⁶⁴Cu decay spectrum were employed to calculate mean absorbed dose rates (Gy/s) at the voxel level. Absorbed doses were derived by integrating residence times, and dose–volume histograms (DVHs) were generated for nodules and organs-at-risk.

Results: The highest absorbed doses per unit activity were observed in the colon (0.1063 mGy/MBq), gallbladder (0.0522 mGy/MBq), and liver (0.0475 mGy/MBq). Tumor nodules exhibited heterogeneous absorbed doses (0.0287 vs. 0.0083 mGy/MBq), influenced by surrounding organ activity. DVHs provided insight into dose heterogeneity, highlighting regions receiving elevated doses compared with organ means.

Conclusion: In this study, a voxel-level Monte Carlo–based dosimetry framework for [⁶⁴Cu]Cu-DOTATOC PET/CT imaging was implemented and applied to a patient-specific

dataset. The results demonstrate the capability of the proposed method to estimate spatial absorbed dose distribution and generate dose–volume histograms for organs and nodules. Future studies with multi-timepoint imaging and larger patient cohorts are warranted.

Keywords: Copper-64; DOTATOC; Voxel-based dosimetry; Monte Carlo simulation; PET/CT

INTRODUCTION

Copper-64 labeled DOTATOC ([⁶⁴Cu]Cu-DOTATOC) has gained significant attention as a versatile radiopharmaceutical agent for the imaging and treatment of neuroendocrine tumors (NETs) due to its high affinity for somatostatin receptors, which are predominantly overexpressed in these tumors [1]. The conjugation of the somatostatin analog DOTATOC with the radionuclide Copper-64 enables targeted delivery that utilizes Cu-64's emission of positrons for high-resolution PET imaging [2].

The physical properties of Cu-64, notably its half-life of approximately 12.7 hours, create an advantageous balance that allows extended imaging and dosimetry assessments compared to the commonly used shorter-lived isotopes such as Gallium-68. This extended half-life enables comprehensive pharmacokinetic analysis, including long-term bio-distribution and clearance profiles, which are essential for accurate radiation dose estimation to tumors and normal tissues [3].

Also the lower positron range of [⁶⁴Cu]Cu-DOTATOC than of [⁶⁸Ga]Ga-DOTATOC theoretically leads to a better spatial resolution.[1] On the other hand, the beta particles emitted by Cu-64 can be toxic and potentially harmful to healthy organs. Therefore, dosimetry is essential for optimizing [⁶⁴Cu]Cu-DOTATOC applications, as it provides quantitative data for imaging [4]. Clinical and preclinical investigations highlight how [⁶⁴Cu]Cu-DOTATOC PET enables enhanced tumor detection, which are paramount for predicting therapeutic outcomes. The theranostic integration of Cu64-DOTATOC epitomizes precision medicine in nuclear oncology by enabling dosimetry tailored to the patient's unique tumor and organ characteristics [5-7].

This study aims to perform voxel-based dosimetry for Cu64-DOTATOC using the Monte Carlo simulation method implemented in the GATE code. This approach allows detailed three-dimensional dose calculations with high spatial resolution, improving the accuracy of dose estimations in complex anatomical structures and heterogeneous tissues, ultimately facilitating more effective and personalized radionuclide therapy.

METHODS

Imaging protocol

PET/CT imaging was conducted on a 16-slice, 5-ring GE Discovery IQ system (BGO-based) at 1 and 24 hours post-injection of [⁶⁴Cu]Cu-DOTATOC (0.05 mCi/kg). To ensure voxel-level quantitative accuracy, the PET scanner was cross-calibrated quarterly with the dose calibrator per NEMA NU-2 standards. PET data (192×192 matrix) were reconstructed using Q.Clear (block-sequential regularization) and OSEM with point-spread-function (SharpIR/VUE Point HD) with 4 iterations and 12 subsets and a Gaussian filter with 6.4 mm cut-off, ensuring full convergence and optimized signal-to-noise ratio. Co-registered CT scans (120 kV, modulated 10–300 mAs, 512×512 matrix, 3.75 mm slice thickness) were reconstructed via ASiR (Adaptive Statistical Iterative Reconstruction) to provide attenuation and scatter corrections. Finally, reconstructed PET values were converted to decay-corrected activity concentrations (Bq/mL), accounting for branching ratios to facilitate precise voxel-based dosimetry.

Above mentioned dose of [⁶⁴Cu]Cu-DOTATOC was administered intravenously. To allow for distribution and uptake of radiotracer, the patient was allowed to rest for 60 min in a shielded

room. Imaging was performed on an integrated 16-slice PET/CT scanner. CT scanning was performed for attenuation correction and localization purposes. 3D emission scan was acquired. Images were reviewed in the trans-axial, coronal, and sagittal planes. Maximum intensity projection (MIP) view of [^{64}Cu]Cu-DOTATOC distribution in patient at 1 and 24 hours after injection are shown in Figure1.

Dosimetry

Pre-processing of data: The CT images were used as the reference for organ delineation. Initial whole-body organ segmentations were generated automatically using a deep learning-based framework implemented in MONAI. The resulting masks were then imported into 3D Slicer, where they were carefully reviewed and manually refined by an experienced specialist. Substantial manual corrections were applied to ensure accurate organ boundaries and to adapt the segmentations for dosimetry simulations. The final refined segmentations used in this study are illustrated in Figure 2.

Monte Carlo simulation: The GATE Monte Carlo framework (version 8.1) was used for dosimetry. As mentioned, phantom and source are necessary to run a Monte Carlo simulation in GATE. The simulations were validated in our previous work [8]. The attenuation-phantom (phantom) was the CT image of the patient, and the source-phantom (source) was the PET image. For the purpose of inserting a PET-CT image in GATE firstly the image should be converted to MetaImage image file format. 3D Slicer saves the image as a header file (.mhd) plus a raw data file (.raw). Secondly we converted the Hounsfield Units (HU) of the CT image to materials in GATE. Then for radiation transport simulation the energy spectra of ^{64}Cu were derived from MIRD data [9]. As shown in Figure 3, the decay of ^{64}Cu , including all relevant emissions (beta, photons, and monoenergetic electrons), was simulated. To achieve more accuracy, “standard physical processes” were used to perform the simulation, which included Photoelectric, Compton, Rayleigh scattering, Gamma Conversion, Electron Ionization, Bremsstrahlung, and Multiple Scattering processes. The output files from the simulation include the mean absorbed dose rate (Gy/s) and the corresponding uncertainty files. The total number of decays simulated was chosen to obtain a statistical uncertainty less than 3%.

Time-activity curve: Time-activity curves were derived from the dual-time-point PET/segmented CT images (1 h and 24 h post-injection). Due to the limited number of imaging time points, a mono-exponential model was applied to characterize the effective clearance kinetics of the radiopharmaceutical in organs at risk and lesions. The effective decay constant obtained from the fit was used for residence time estimation and subsequent absorbed dose calculations.

Calculation of absorbed dose: After completing the above steps, the mean absorbed dose to each organs can be calculated by multiplying the GATE output, mean absorbed dose rate (Gy/s), with the residence time of the radiopharmaceutical. Finally, the mean absorbed dose to organs and nodules from [^{64}Cu]Cu-DOTATOC and Also the Dose-Volume Histogram (DVH) curves are calculated.

RESULTS

Time-activity curves were generated from the dual-time point PET/Segmented-CT images and fitted by 2 compartment exponential equation for consideration of fast and slow decreasing of radiopharmaceutical in organs at risk or nodules, as shown in Figure 4.

After completing the above steps, the mean absorbed dose to each organs can be calculated by multiplying the GATE output, mean absorbed dose rate (Gy/s), with the residence time of the

radiopharmaceutical. Table 1 summarizes the key dosimetric parameters for selected clinically relevant organs-at-risk and nodules. The reported parameters include segmented volume, activity measured at 1 h and 24 h post-injection, estimated residence time, and mean absorbed dose following [⁶⁴Cu]Cu-DOTATOC administration. Also the Dose-Volume Histogram (DVH) curves are shown in Figure 5. The calculated absorbed doses were within the range of previously reported human dosimetry data for ⁶⁴Cu-labeled somatostatin analogues. The mean absorbed dose to the kidneys was approximately 0.03 mGy/MBq, which is consistent with published values (~0.02–0.04 mGy/MBq) [10]. The liver absorbed dose (0.0475 mGy/MBq) and spleen absorbed dose (0.0212 mGy/MBq) were also comparable to previously reported ranges [10]. Similarly, the urinary bladder absorbed dose (0.0263 mGy/MBq) was in agreement with literature data. These findings support the consistency of our Monte Carlo-based voxel dosimetry framework with established organ-level dosimetry results. The relatively lower absorbed dose observed in nodule-2 compared to nodule-1 may partly be influenced by differences in lesion size and potential partial volume effects. To better illustrate the spatial distribution of absorbed dose, a fused voxel-level dose map overlaid on the CT images is presented in Figure 6. The coronal, sagittal, and transverse views at 1 hour post-injection demonstrate the heterogeneous distribution of absorbed dose across organs and lesions. Higher dose regions correspond to areas of increased radiotracer uptake, while lower dose regions reflect reduced activity concentration. This spatial visualization complements the quantitative DVH analysis and highlights intra-organ and intra-lesion dose heterogeneity.

DISCUSSION

In this study, the dosimetry of Copper-64 labeled with DOTATOC was done by Monte Carlo simulation method. The organ absorbed doses obtained in this study were quantitatively consistent with previously published human dosimetry data of ⁶⁴Cu-labeled somatostatin analogues. In particular, the mean kidney absorbed dose (~0.03 mGy/MBq) was within the reported range of approximately 0.02–0.04 mGy/MBq in clinical PET dosimetry studies. Similarly, the liver (0.0475 mGy/MBq), spleen (0.0212 mGy/MBq), and urinary bladder (0.0263 mGy/MBq) absorbed doses were comparable to values reported in the literature [10]. This agreement suggests that the absorbed dose estimates derived from our voxel-based Monte Carlo framework are consistent with established organ-level dosimetry approaches. It should be emphasized that the primary advantage of the proposed method is not the claim of superior absolute accuracy over conventional MIRD/OLINDA-based dosimetry, but rather its ability to provide spatial dose distribution and dose–volume histogram (DVH) analysis at the voxel level. This allows assessment of intra-organ dose heterogeneity, which cannot be evaluated using organ-averaged approaches. Although a comprehensive external validation of the entire patient-specific workflow—including PET quantification accuracy, segmentation, time–activity curve modeling, and residence time estimation—was beyond the scope of this study, the consistency of our results with previously published human data supports the reliability of the implemented framework. Future studies including larger patient cohorts and additional imaging time points are required for further validation.

Considering that the high-energy beta particles of Copper-64 can deliver a significant dose to tissue, the importance of dosimetry in its application is substantial [11]. With the aid of PET/CT images and Monte Carlo method, we were able to investigate the distribution of absorbed dose within various healthy and abnormal organs at the voxel level and arrive at the volumetric dose distribution, known as DVH. The significance of this work lies in our ability to estimate the percentage of the volumetric dose to healthy organs, allowing us to determine whether the dose has exceeded the permissible limit for those organs. Conventional dosimetry methods, such as the MIRD method, focus only on the average dose of an organ, whereas we know that the mean dose to an organ or tumor alone is not adequate for treatment evaluation [12]. In this dosimetry

approach, we can access different volumetric percentages of the absorbed dose for various organs with the help of the DVH curve, which can aid in evaluating the treatment process. The observed differences in absorbed dose between nodules may be due to cross-dose from surrounding organs, resulting from their varying positions. Additionally, the high absorbed dose in the colon can be attributed to the excretion of the radiopharmaceutical through the intestines. However, based on the DVH curve, it can be inferred that this absorbed dose is heterogeneous, which is also a result of the positioning and movement of the radiopharmaceutical along the intestines until its excretion. Limitations of this study include the absence of more time point of imaging and residence time calculation for more accurate dosimetry calculations and non-RBE-based absorbed dose calculation, which should be addressed in future work. An additional limitation of this study relates to partial volume effects (PVE), particularly for small lesions. Due to the limited spatial resolution of PET imaging, activity concentration in small nodules may be underestimated as a result of spill-out effects. No explicit partial volume correction was applied in the present analysis. Therefore, the absorbed dose values and DVH metrics reported for small nodules may represent conservative (potentially underestimated) estimates. The impact of PVE is expected to lessen as lesion size increases; however, for sub-centimeter structures, this effect may be substantial [13]. Future studies should incorporate recovery coefficient-based correction methods or resolution modeling techniques to enhance quantitative accuracy in small lesions.

CONCLUSION

In this study, a voxel-level Monte Carlo-based dosimetry framework for [⁶⁴Cu]Cu-DOTATOC PET/CT imaging was implemented and applied to a patient-specific dataset. The results demonstrate the capability of the proposed method to estimate spatial absorbed dose distribution and generate dose-volume histograms for organs and nodules. However, since this study was based on a single patient and limited imaging time points, the findings should be considered preliminary. Further validation in larger patient cohorts and with more comprehensive imaging protocols is needed to assess reproducibility, quantitative robustness, and potential clinical applications.

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Table1. Summary of dosimetric parameters for selected clinically relevant organs-at-risk and nodules following [⁶⁴Cu]Cu-DOTATOC administration. The table reports segmented volume (cc), activity at 1h and 24hrs post-injection (kBq), estimated residence time (h), and mean absorbed dose (mGy/MBq)

Organ	Volume (cc)	Residence time (h)	1 hr Activity (kBq)	24 hrs Activity (kBq)	Mean Absorbed Dose (mGy/MBq)
Spleen	108.7	9.2	10.288	0.838	0.021
Right kidney	200.3	11.6	11.155	1.532	0.030
Left kidney	191.0	11.2	11.487	1.487	0.030
Gallbladder	27.0	53.4	3.273	3.257	0.052
Liver	1417.5	28.6	6.565	3.105	0.047
Stomach	321.2	22.7	2.437	0.905	0.019
Aorta	190.5	17.5	1.368	0.369	0.008
Inferior vena cava	64.6	18.6	1.844	0.539	0.012
Portal vein and splenic vein	19.8	19.7	3.082	0.972	0.019
Pancreas	43.3	17.4	2.494	0.668	0.013
Right adrenal gland	1.8	16.2	3.757	0.908	0.018
Left adrenal gland	4.9	17.2	2.910	0.767	0.015
Superior lobe of left lung	452.0	14.2	0.945	0.187	0.010
Inferior lobe of left lung	353.5	14.4	1.459	0.296	0.013
Superior lobe of right lung	395.7	14.7	0.927	0.194	0.010
Middle lobe of right lung	95.7	15.7	1.414	0.328	0.014
Inferior lobe of right lung	405.7	19.	1.584	0.502	0.019
Nodule-1	3.2	11.6	8.560	1.181	0.029
Nodule-2	1.8	5.6	8.000	1.225	0.008

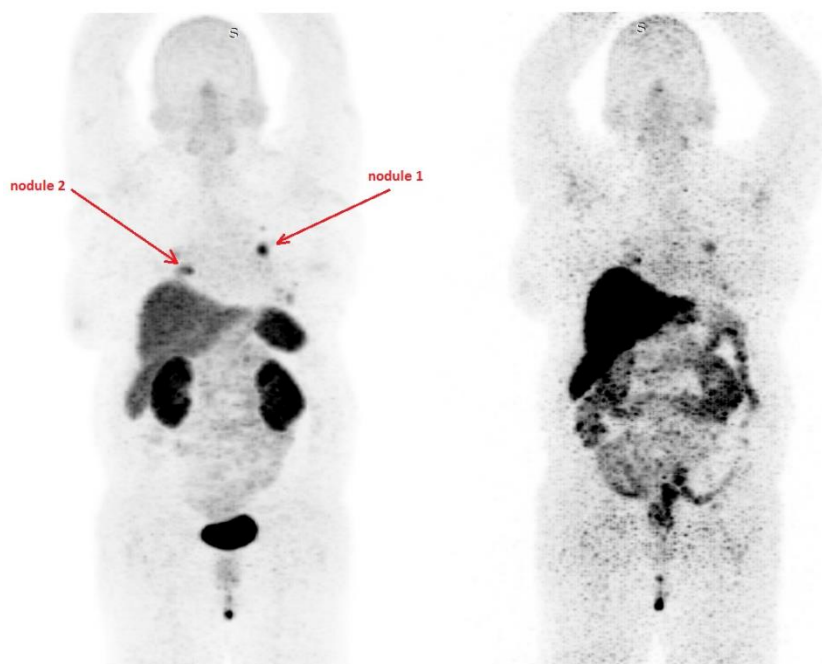


Figure 1. Maximum intensity projection (MIP) view of ^{64}Cu -DOTATOC distribution in patient at 1h (left) and 24 hours (right) after injection

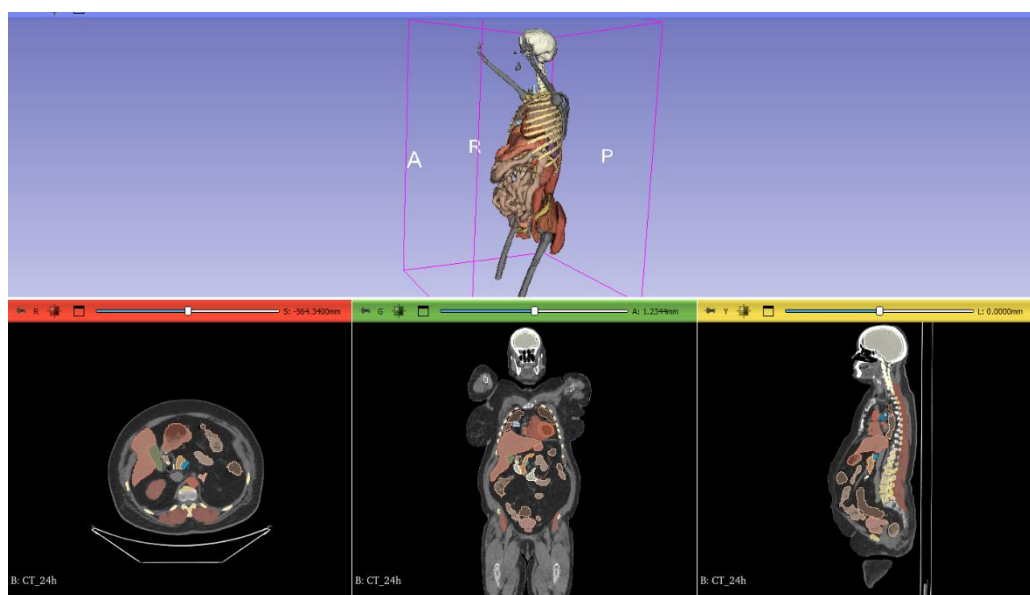


Figure 2. Final organ and lesion segmentations on CT images, generated using a deep learning-based framework and subsequently manually refined in 3D Slicer for dosimetry analysis

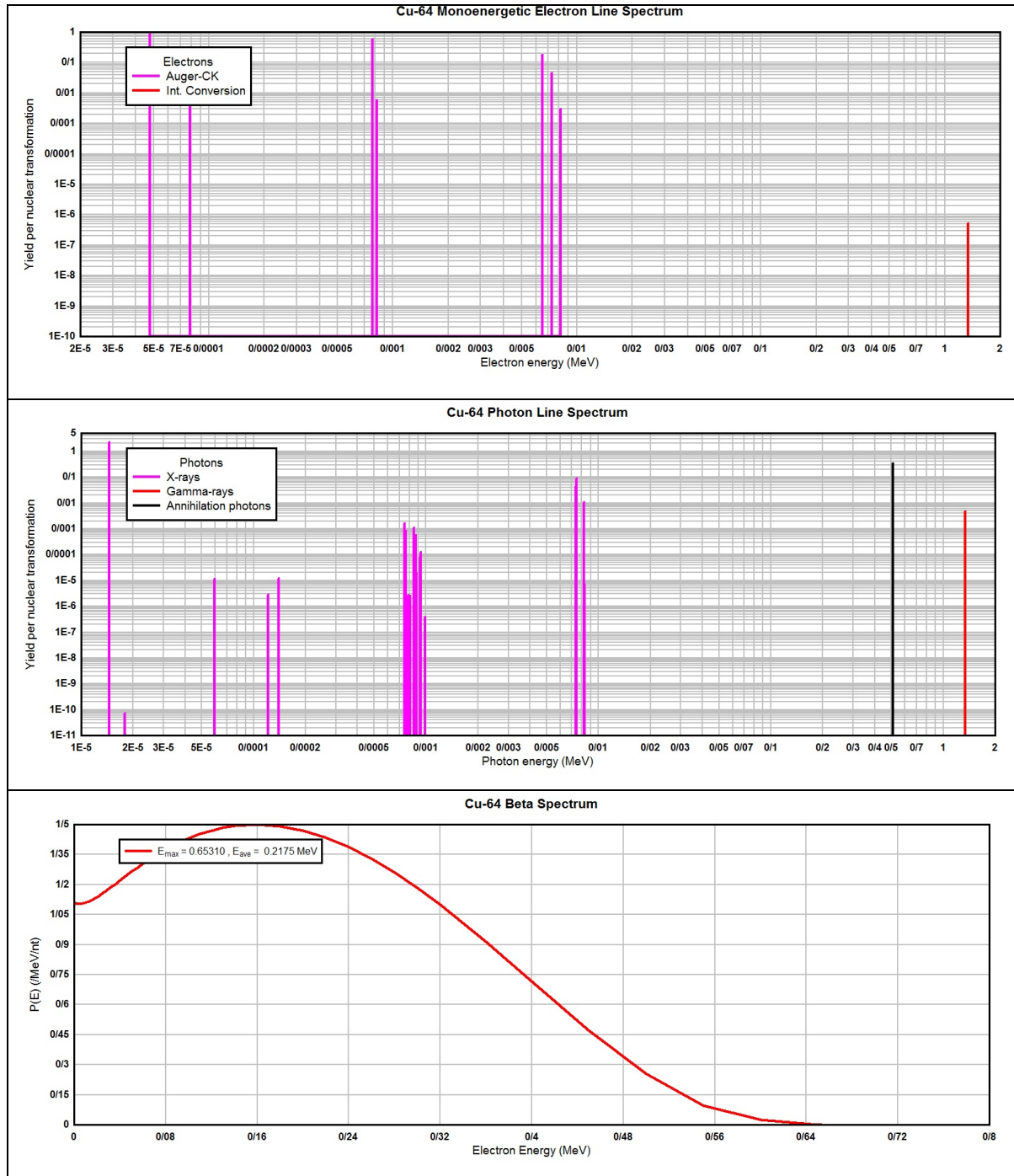


Figure 3. Radiation spectrum of electron, photon and beta beams for ^{64}Cu radionuclide [9]

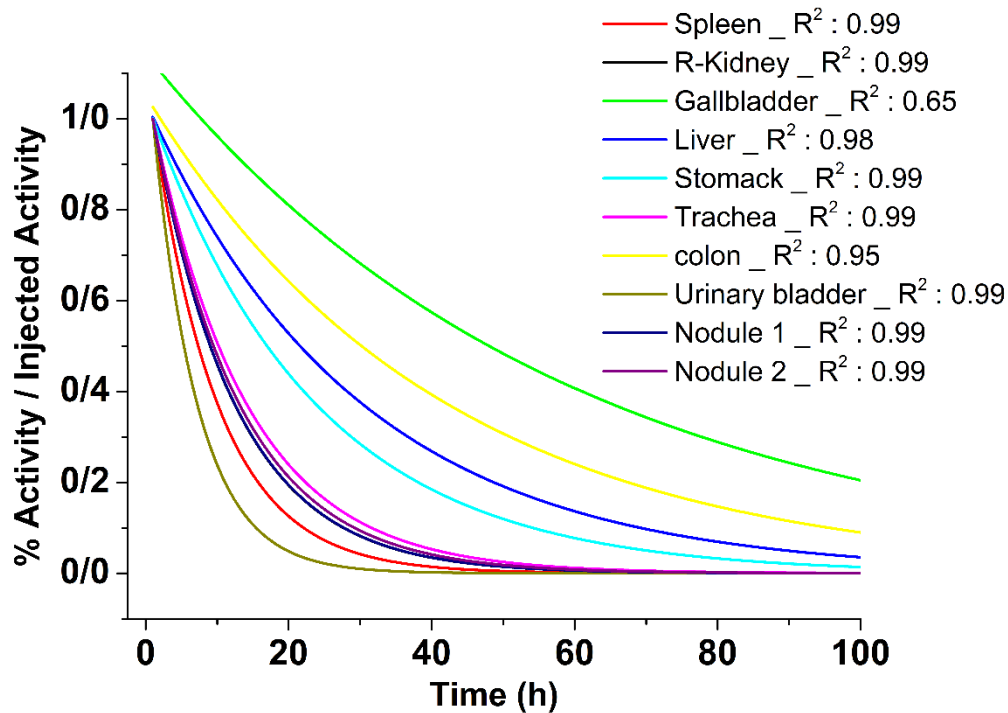


Figure 4. Normalized time-activity curve for most important organs at risk and nodules

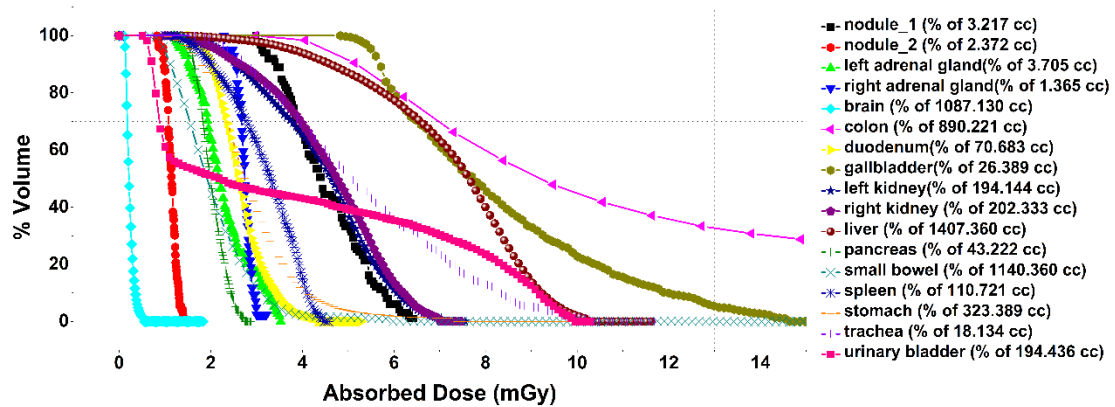


Figure 5. Dose volume histogram (DVH) of 2 detected nodules and organs at risk

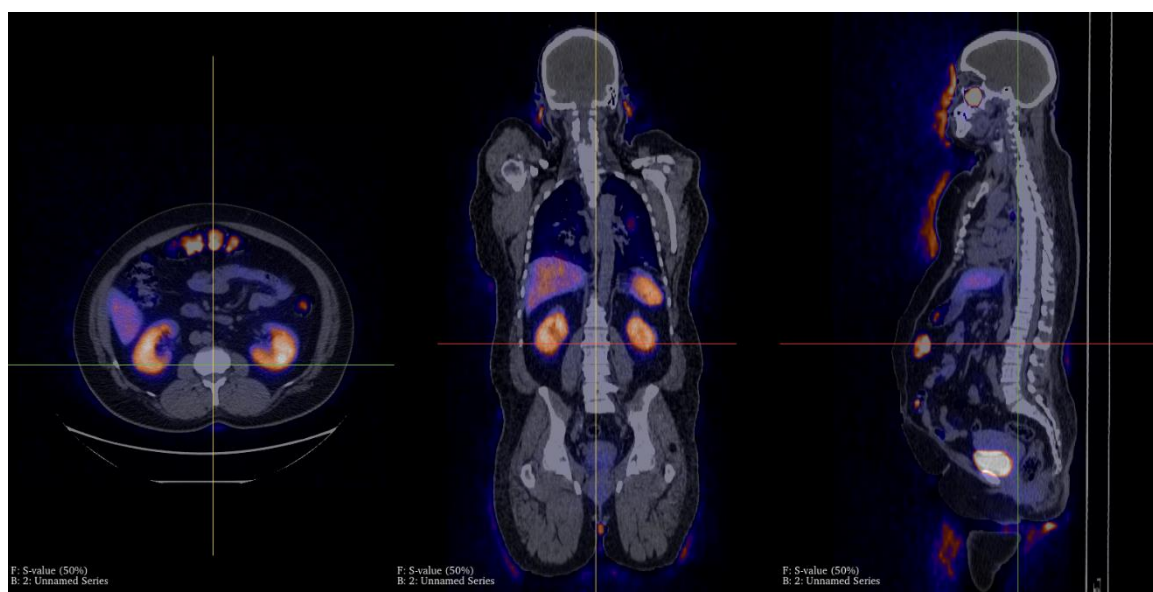


Figure 6. Voxel-based absorbed dose map fused with CT images at 1 hour post-injection. Coronal, sagittal, and axial views demonstrate spatial dose heterogeneity within normal organs and nodules derived from Monte Carlo simulation