Simplified patient-specific renal dosimetry in $^{177}$Lu therapy: a proof of concept

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**ABSTRACT**

**Purpose:** The aim of this proof-of-concept study is to propose a simplified personalized kidney dosimetry procedure in $^{177}$Lu peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors and metastatic prostate cancer. It relies on a single quantitative SPECT/CT acquisition and multiple radiometric measurements executed with a collimated external probe, properly directed on kidneys.

**Methods:** We conducted a phantom study involving external count-rate measurements in an abdominal phantom setup filled with activity concentrations of $^{99m}$Tc, reproducing patient-relevant organ effective half-lives occurring in $^{177}$Lu PRRT. GATE Monte Carlo (MC) simulations of the experiment, using $^{99m}$Tc and $^{177}$Lu as sources, were performed. Furthermore, we tested this method via MC on a clinical case of $^{177}$Lu-DOTATATE PRRT with SPECT/CT images at three time points (2, 20 and 70 hrs), comparing a simplified kidney dosimetry, employing a single SPECT/CT and probe measurements at three time points, with the complete MC dosimetry.

**Results:** The experimentally estimated kidney half-life with background subtraction applied was compatible within 3% with the expected value. The MC simulations of the phantom study, both with $^{99m}$Tc and $^{177}$Lu, confirmed a similar level of accuracy. Concerning the clinical case, the simplified dosimetric method led to a kidney dose estimation compatible with the complete MC dosimetry within 6%, 12% and 2%, using respectively the SPECT/CT at 2, 20 and 70 hrs.

**Conclusions:** The proposed simplified procedure provided a satisfactory accuracy and would reduce the imaging required to derive the kidney absorbed dose to a unique quantitative SPECT/CT, with consequent benefits in terms of clinical workflows and patient comfort.

1. Introduction

Kidneys are among the most irradiated organs during $^{177}$Lu-labelled peptide receptor radionuclide therapy (PRRT) and prostate-specific membrane antigen (PSMA) therapy [1,2]. When personalized dosimetry is applied, the renal absorbed dose is the parameter used to determine the maximum tolerable total activity administration along treatment cycles for a given patient [3,4]. From External Beam Radio-Therapy (EBRT), a cumulated absorbed dose of 23 Gy [5] is adopted to limit the risk of nephrotoxicity within a tolerable level [6]. In absence of more specific dose limits for $^{177}$Lu PRRT and PSMA treatments, this value is assumed for safety.

Treatment optimization, as required by the EC Directive 2013/59/Euratom [7], relying on image-based dosimetry, is possible and would potentially lead to a significantly improved response in patients [3]. Presently, most of the centers providing $^{177}$Lu therapy do not perform treatment optimization based on dosimetry [8,9], mostly because of the complexity of the dosimetry workflow in terms of cost/time and

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resources, which represent one limitation to dosimetry-based treatment optimization. Assuming a fixed activity administration per cycle (typically 7.4 GBq), the number of cycles a given patient would undergo while aiming to reach the kidney absorbed dose limit could be determined [10]. On the other hand, an escalation of administered activity is conceivable by possibly reducing the number of cycles [11].

Image-based renal dosimetry for $^{177}$Lu PRRT (and PSMA) have been reported by many groups so far. Dose estimates were obtained from quantitative imaging at successive time points. Sequential planar imaging, hybrid and full tomographic (SPECT/CT) dosimetry protocols were adopted. Among them, dosimetry protocols based on 3D information (multiple SPECT/CT or hybrid planar + 1 SPECT/CT) have the potential for a better accuracy and reproducibility [3,4,12-14].

Excluding research studies, because of the time and resource burden involved, most clinical dosimetry protocols typically used no more than three image time points. A certain number of studies investigated the possibility of reducing the image acquisition to only one or two SPECT/CT [15-18]. Reducing the number of acquired time samples inevitably reduces the amount of information available to model the patient-specific renal bio-kinetics. Even if it is known that the actual bio-kinetics is characterized by a rapid uptake followed first by a rapid excretion (plasma washout) and then by a slow clearance, typically a single mono-exponential model is assumed to fit this latter one [19]. Reducing to only one acquisition, and compensating with cohort-specific information, inevitably involves a loss of patient-specificity in the estimated dosimetric information, further leading to a possible loss in accuracy and indeed in the level of treatment optimization [20].

The aim of this work is to present a proof of concept of a simplified renal dosimetry workflow, based on multiple time point acquisitions using an external probe complemented by a single quantitative SPECT/CT acquisition of the abdominal region. To do this, we performed an experimental phantom study complemented by Monte Carlo (MC) simulations of the proposed dosimetry protocol. An example of MC- derived kidney dose estimate based on real patient data (three consecutive SPECT/CT) is also presented and compared with the absorbed kidney dose estimated with the proposed simplified protocol. The minimal impact on scanner occupation time, together with the ease of multiple radiometric acquisitions with a probe, commonly available in nuclear medicine departments, has the potential to expand the application of patient-specific treatment optimization based on renal dosimetry in $^{177}$Lu PRRT and PSMA treatments.

2. Materials and methods

We present methodological aspects related to the proposed simplified kidney dosimetry in three subsections. First (Section 2.1), we present a $^{99m}$Tc experiment based on realistic abdomen phantom geometry and effective half-life for selected compartments representing kidneys, liver and intestines. Secondly (Section 2.2), we describe the Monte Carlo simulation of the above experiment, for $^{99m}$Tc and $^{177}$Lu radionuclides. Finally (Section 2.3), we present the test of our proposed methodology to a single PRRT case that was imaged with three SPECT/CT scans.

2.1. Phantom experiment

We tested the proposed simplified methodology in a phantom study, providing a controlled geometry with known activities in abdominal organ compartments. We used an abdominal phantom (commercial Kyoto Liver/Kidney phantom, Nuclmed, Roeselare, Belgium) containing a liver insert of 1760 ml, two kidney inserts (left and right) with volumes of 155 and 160 ml, respectively, included in the main volume of 15 L. The main volume was filled with non-radioactive water to reproduce photon attenuation typical of soft tissues. Without a specific phantom compartment representing the intestines within the main phantom volume, we positioned a 200-ml bottle with a specific activity concentration (Ac) outside, in the anterior position, along the posterior/ anterior direction defined by the collimated geometry of the dose rate measures. The liver insert also contained three spherical inserts (visible in Fig. 1) having 48 ml of total volume, that in the present configuration were filled with water and no radioactivity.

For ease of accessibility, cost concerns and radioprotection reasons related to the need of voiding and filling the phantom at each experimental realization (ER), we filled the abdominal compartments (such as the kidney, the liver and the intestine) with activities of $^{99m}$Tc.

We filled the phantom four times so as to reproduce the relative uptakes of compartments at four instants after administration (24, 48, 72 and 168 hrs). Each Experimental Realization (referred as ER1, ER2, ER3 and ER4) reproduced relative organ activities at the considered moments compatible with the median effective $^{177}$Lu DOTATATE organ half-lives listed in Marin et al. [21], namely 55 hrs for the kidneys, 79 hrs for the liver, and 85 hrs for the intestines. In the absence of more specific information, the effective half-life of the remainder of the body (85 hrs) was assumed for the intestines. The activity concentration in each organ was set to have an initial ratio of three to one between the kidneys and the liver and six to one between the kidneys and the intestines. As the bottle for the intestinal activity could not be placed inside the phantom, its initial Ac was chosen to compensate for 10 cm of attenuation in water present between the center of the 200 ml external compartment and the ideal intestine position inside the main phantom volume. Table 1 lists the total activities and activity concentrations used for each of the ERs. We adopted relative Ac ratios between organs based on experience gathered in our center, which also correlates with values extrapolated from published data [12,22-24].

$^{99m}$Tc activities in syringes used to fill the different compartments were measured in a Veenstra activimeter (Veenstra VDC-405, COMECER Netherlands) available in our Institution. The calibration of the activimeter is periodically verified by a certified national metrology service from the Institute of Radiation Physics in Lausanne (Switzerland). We considered the error of the activity determination by the activimeter we used to be within 5% of the measured value.

For each ER, we measured from the posterior side the count rate (CR) from two different locations of the left kidney, located at 2 cm above and 2 cm below the kidney midplane (positions L-UP and L-DN respectively, as indicated in Fig. 1a). For each ER and acquisition location (L-UP and L-DN), we performed three consecutive measurements; indeed we considered the average value.

The left kidney was chosen as the most favourable location for the measurements because of its overall reduced overlap with other organs (typically the liver) compared to the right kidney.

In parallel to the collimated measures on the left kidney, we performed up and down CR measurements corresponding to the middle point between the two kidneys (M–UP and M–DN, positions as indicated in Fig. 1a). We used these latter measurements to evaluate the background count-rate contribution ($C_{\text{bg}}$) to be subtracted from the respective kidney CR, in order to obtain background-corrected count-rate ($C_{\text{CR,corr}}$).

An Automess 6150 CE-6 dose rate meter equipped with the contamination probe (Automess 6150 CE-17) was employed. The probe was shielded against stray irradiation by a cylindrical cap made of lead, expressly machined to host the AD-17 probe inside (inner cylinder diameter 17 mm, outer diameter 20 mm, total length 90 mm). The front wall of the cylinder was 20-mm thick (<0.01% of transmission for 208 keV gamma emission from $^{177}$Lu), with a circular hole (10 mm diameter) defining the cone of view of the measurement (see Fig. 2 below).

The effective half-life ($T_{\text{eff}}$) of the kidney was estimated by fitting with a mono-exponential function the mean values of count rates, obtained from the four ERs, corrected for background and also without background correction. The Supplementary Materials provide full details about the statistical analysis.
2.2. Monte Carlo simulation of the phantom set-up

We used Monte Carlo simulations to reproduce the phantom experiment with $^{99m}$Tc described above. Then, simulations were extended to $^{177}$Lu. We used GATE [25,26] version 9.0, relying on GEANT4 [27,28] version 10.05.p01, a general-purpose MC package widely employed in the field of medical radiation physics and, particularly, in internal dosimetry of radiopharmaceuticals [29-31].

The experimental set up was implemented in the MC as a composition of a voxelized volume representing the abdominal phantom with liver and kidneys inserts, and multiple geometric volumes resembling the detector-collimator geometry for the detector plus the outer bottle representing the intestines (Fig. 2).

2.2.1. Geometry of the phantom set-up

The voxelized phantom was defined starting from a CT scan of the abdominal phantom. The CT image was resized and resampled using 3DSlicer [32,33], employing ResampleImageFilter module with Lanczos interpolation [34], in order to restrict the simulations to the volume of interest for the study. The final image had a resolution of $156 \times 157 \times 101$ voxels, with voxel sizes of $2.0 \times 2.0 \times 2.0$ mm$^3$.

In GATE, materials and densities were assigned to each voxel via Automated Hounsfield Units (HU) stoichiometric calibration [35]. This method uses the interpolation of a HU-density calibration relation to assign given chemical compositions on the basis of user-defined intervals, and assigns densities on the basis of sub-intervals defined in such a way that they differ from each other for a user-defined value (called “density tolerance”), that in our study was set 0.01 g/cm$^3$.

CT scale is optimized for human tissues and saturates at 3071 Hounsfield units (HU) on typical CT images [36]. The metal screws contained in our phantom exhibit this kind of saturation, and the correct material and density in the corresponding voxels were assigned manually.

Table 3 outlines the materials defined for the simulations and their respective density intervals.

Objects external to the abdominal phantom were defined as geometric volumes. The bottle used to represent the intestines was defined as a hollow cylinder of PMMA with 2.5-mm thick walls, containing 200 mL of water. The shielding collimator was generated by combining cylindrical volumes and setting lead as their material. The detector volume was modelled as a water cylinder with a diameter equal to the Automess 6150 CE-6 external diameter, placed inside the collimator according to the experimental position. The electrodes of the dose rate meter were modelled as a cylindrical plate of aluminium with small lateral walls, whose dimensions and position in the detector volume were deduced from a dedicated CT scan of the probe. The active volume of the detector was defined with the same dimensions and position as in the instrument (27.2 mm of diameter, 0.8 mm of height), deduced also in this case from the dedicated CT scan.

We simulated two detector positions for each ER, namely the detector centered on the left kidney, in a vertical position at the midpoint.
between L-UP and L-DN, and the detector centered between the kidneys, in a vertical position at the midpoint between M–UP and M–DN (Fig. 1b). Hereafter we will refer to them as simply L and M configurations, respectively. Fig. 2 details the implemented geometry.

2.2.2. Primary sources and simulation settings

For both L and M configurations, four activity source regions were defined, corresponding to the liver, the right kidney, the left kidney, and the bottle. These sources were separately simulated, to properly account for individual contributions to the detector output and related uncertainties.

The liver and the kidneys, being inside the abdominal phantom, were defined as voxelized sources, properly segmented through 3DSlicer. Uniform distributions of activity were simulated inside these regions, similarly as in [38]. The bottle resembling the intestines was instead defined as a geometric cylindrical source with uniform activity.

Table 2:
The HU-density calibration points employed for voxelized phantom density definition

<table>
<thead>
<tr>
<th>HU</th>
<th>Density (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1000</td>
<td>0.0012</td>
</tr>
<tr>
<td>-750</td>
<td>0.2512</td>
</tr>
<tr>
<td>-500</td>
<td>0.5012</td>
</tr>
<tr>
<td>-250</td>
<td>0.7512</td>
</tr>
<tr>
<td>0</td>
<td>1.0012</td>
</tr>
<tr>
<td>150</td>
<td>1.0767</td>
</tr>
<tr>
<td>520</td>
<td>1.2661</td>
</tr>
<tr>
<td>890</td>
<td>1.4554</td>
</tr>
<tr>
<td>1260</td>
<td>1.6447</td>
</tr>
<tr>
<td>1630</td>
<td>1.8340</td>
</tr>
<tr>
<td>2000</td>
<td>2.0233</td>
</tr>
</tbody>
</table>

Fig. 2. Axial view of L (a) and M (b) configurations implemented in the MC geometry, sagittal view (c) referred to both configurations and a 3D representation of the system in L configuration (d). In MC, A = 62 mm for L, A = 0 mm for M; B = 90 mm for both M and L, since in the experiment L–UP and M–UP had B = 110 mm, L–DN and M–DN had B = 70 mm; C = 55 mm in MC for both L and M.
Table 3
Materials [37] used for the phantom study simulations, and their corresponding density intervals set in GATE.

<table>
<thead>
<tr>
<th>Material</th>
<th>Density interval ρ (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>ρ ≤ 0.40</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>0.40 &lt; ρ ≤ 0.92</td>
</tr>
<tr>
<td>Water</td>
<td>0.92 &lt; ρ ≤ 1.05</td>
</tr>
<tr>
<td>PMMA (polymethyl methacrylate)</td>
<td>1.05 &lt; ρ ≤ 2.02</td>
</tr>
<tr>
<td>Aluminium</td>
<td>2.02 &lt; ρ ≤ 6.11</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>ρ &gt; 6.11</td>
</tr>
</tbody>
</table>

distribution.

Simulations were performed using $^{99m}$Tc and $^{177}$Lu as radionuclides. $^{99m}$Tc was simulated as a 140.511-keV source of gamma photons. $^{177}$Lu was simulated as an ion source using Neutrondecay GEANT4 module, which includes the full emission spectrum of beta and mono-energetic electrons, and gamma and X photons.

For each source, radionuclide and detector configuration, the simulation was split into two steps:

1) First, the complete geometry of the experimental measurement was set, namely phantom, detector, collimator and bottle. The decay of radionuclides, uniformly distributed inside the selected source organ, and the transport and interaction of daughters in the whole world were simulated, using G4EmStandardPhysics_option3 GEANT4 physics list. The phase space of particles passing through the collimator hole was scored (in the green volume shown in Fig. 2) and saved in a ROOT file.

2) Second, the geometries of only the detector and collimator were set, and the phase space file produced in step 1) was used as the source to simulate, with high statistics, the photons collimated through the hole. The energy deposited in the detector active volume was scored with the GATE DoseActor.

Two independent simulations for each source, radionuclide and configuration were performed, to take into account the uncertainties produced by the effect of phase space scoring on the deposited energy outcome, as explained in the Supplementary Materials, since the collimated particles reaching the detector represent “rare events” with respect to the total events in a simulation.

2.2.3. MC output analysis and half-life estimation

Outcomes reproducing all four ERs for the two nuclides were deduced in terms of deposited energies per event ($\epsilon$), according to the following procedure. Indicating the source region with “s”, the configuration (L or M) with “c”, the ER (corresponding to the four time points) with “t”, the energy deposited in the probe active volume with $E_{\text{sc}}(t)$ in a simulation employing $N_{\text{sc}}(t)$ primary events in the first step and $K_{\text{sc}}(t)$ events in the second step, the energy deposited per event in the probe active volume, $\epsilon_{\text{sc}}(t)$, was deduced as:

$$\epsilon_{\text{sc}}(t) = \frac{E_{\text{sc}}(t) \cdot P_{\text{sc}}(t) \cdot A_{\text{F}}(t)}{K_{\text{sc}}(t)},$$

where $P_{\text{sc}}(t)$ is the phase space entries ($P_{\text{sc}}(t)$) per event in the first step,

$$P_{\text{sc}}(t) = \frac{P_{\text{sc}}(t)}{N_{\text{sc}}(t)},$$

and $A_{\text{F}}(t)$ is the activity fraction, i.e., the ratio between the activity $A_{\text{s}}(t)$ in a source region for a specific ER (Table 1) and the sum of the activities of the four source regions for ER1 ($t = 24$ hrs)

$$A_{\text{F}}(t) = \frac{A_{\text{s}}(t)}{\sum_i A_{\text{s}}(24\text{hrs})}.$$

$N_{\text{sc}}(t)$, both for $^{99m}$Tc and $^{177}$Lu, was set equal to $2 \cdot 10^8$ for the simulations having left kidney as source, and equal to $10^9$ in the case the other sources; these values guaranteed at least 8000 $P_{\text{sc}}(t)$ entries in the sampled phase space for all the first step simulations.

$K_{\text{sc}}(t)$ was instead set equal to $2 \cdot 10^8$ in all the simulations using $^{99m}$Tc, and equal to $5 \cdot 10^8$ in all the simulations using $^{177}$Lu, in order to obtain $\epsilon_{\text{sc}}(t)$ values with relative statistical uncertainties below 0.2%.

In the case of $^{99m}$Tc, simulated as a source of 140.511 keV gammas, the $\epsilon_{\text{sc}}(t)$ values were furtherly weighted by the Branching Ratio (B.R.) of 140.511 keV gamma emission, B.R. = 0.89 [39].

For both configurations, the total energy deposited in the probe sensitive volume at time t, $\epsilon_{\text{sc}}(t)$, is obtained by adding the deposited energies due to each source organ at time t,

$$\epsilon_{\text{sc}}(t) = \sum_{s} \epsilon_{\text{sc}}(t).$$

For each time, the background-corrected total energy deposited per event, $\epsilon_{\text{corr}}(t)$, was calculated as:

$$\epsilon_{\text{corr}}(t) = \epsilon_{\text{sc}}(t) - \epsilon_{\text{b}}(t).$$

The effective half-life ($T_{\text{eff}}$) in the left kidney was estimated by fitting with a mono-exponential function the four $\epsilon_{\text{corr}}(t)$ obtained at $t = 24, 48, 72$ and 162 hrs. $T_{\text{eff}}$ was moreover calculated by fitting $\epsilon_{\text{sc}}(t)$, i.e., without background correction, at the four aforementioned times.

Since, as stated in the previous Section, two independent simulations were performed for each source, radionuclide and configuration, the fit procedure was applied to multiple combinations of $\epsilon_{\text{corr}}(t)$’s (or of $\epsilon_{\text{sc}}(t)$’s, when not considering background correction), as detailed in the Supplementary Materials, deducing from them the average effective half-life ($T_{\text{eff}}$) and the corresponding Standard Deviation (SDM). Furthermore, in order to test the accuracy of a simplified measurement protocol, several combinations of three among the four time points were selected and fitted, and corresponding $T_{\text{eff}}$ were compared and discussed. Finally, we repeated the aforementioned analysis by excluding in $\epsilon$ the contribution from the bottle source resembling the intestines, to simulate the case of a negligible uptake in it.

2.3. Monte Carlo test on a $^{177}$Lu-DOTATATE PRRT clinical case

We tested our proposed simplified method for $^{177}$Lu kidney dosimetry on a clinical case of $^{177}$Lu-DOTATATE PRRT, for which three SPECT/CT scans were acquired at 2, 20 and 70 h post therapeutic administration. We used them as input in GATE V9.0 MC simulations, to score dose rate values in the kidneys and deposited energies in the detector probe. The probe signal was scored using the same method adopted in the MC simulations of the phantom study, with simulations in L and M configurations at each SPECT time point. Patient-specific MC data were used to derive and compare absorbed doses to the kidneys, using an image-based dosimetry workflow (using the three SPECT/CT available) and the proposed simplified kidney dosimetry, based on external probe measurements and only one quantitative SPECT/CT.

2.3.1. Simulation setting

The simulation set up consisted of the detector with collimator, defined as in Sec. 2.2.1, and of a voxelized volume representing the patient abdomen, defined from the CT scan. For each time point, a voxelized activity source map was defined from the SPECT scan.

The three SPECT/CT scans were mutually registered with 3DSlicer Transformation module, using the scan at 2 hrs as a reference. Rigid linear transforms centered on the left kidney were used.

All the registered images were resized and resampled in order to restrict the volume size to the patient’s body only, to exclude the patient’s bed that would not be present during a probe measurement.

The resampling was carried out using 3DSlicer ResampleImageFilter module adopting Lanczos interpolation. The resolution set for SPECT and CT images was $420 \times 285 \times 112$, with voxel size $1.0 \times 1.0 \times 3.5$ mm$^3$.

The material assignment in the patient was performed, as described in Sec. 2.2.1, with the tissue compositions and density intervals presented in Table 4.

The positions of the detector and collimator volumes with respect to
the voxelized phantom for L and M configurations were coherent to the phantom setting, i.e. L pointing to the midpoint of the left kidney from the back, and M pointing to the midpoint between the kidneys, from the back as well, as depicted in Fig. 4a (and analogously to Fig. 2, with voxelized volume size and distances A, B, C adapted to the present case).

The voxelized activity source was defined for each time point, using the corresponding SPECT scan.

Simulations were performed using $^{17^7}$Lu as radionuclide, defined as in Section 2.2.2. For each time point and configuration, the simulation performed was split into two steps, similar to the phantom study:

1) The first step involved setting the complete geometry: the patient phantom, detector and collimator. Next, the decay of $^{17^7}$Lu distributed according to the SPECT, and the transport and interactions of its daughters in the world were simulated, scoring the phase space of particles passing through the collimator hole, as explained in Section 2.2.2. The absorbed dose map (and dose squared map for the statistical uncertainty evaluation, detailed in Supplementary Materials) in the patient volume was scored, with the same spatial resolution as the CT, using GATE DoseActor.

2) The second step was the same as step two described in Section 2.2.2.

Three independent simulations for each time point and configuration were performed for uncertainty calculation purposes (see Supplementary Material). The left kidney volume of interest (VOI) (Fig. 4) was segmented with 3DSlicer on each CT used, for the half-life estimation and the dosimetric calculations.

2.3.2. Half-life estimation and dosimetric calculations

The energy deposited per event in the probe active volume, \( e(t) \), was deduced in the same way as reported in Eq. (1), considering that in the patient study the subscript “s”, and therefore also Eq. (4), are unnecessary since they were the radionuclide decays distributed according to the entire SPECT image.

Moreover, \( A(t) \) now represents the ratio between the total activity \( A(t) \) in the SPECT at time \( t \) and the total activity in the SPECT at the first time point, \( A(t = 2 \text{ hrs}) \).

The number of primary events in all the first step simulations was set equal to \( 2 \cdot 10^6 \), a value that ensured at least \( 3 \cdot 10^4 \) phase space entries in all the simulations, and average relative statistical uncertainties on the dose map voxels (\( \sigma_e/D_e(t) \) in the Supplementary Materials, Sec. S2.2) within left kidney VOI below 9% in all the simulations. The number of primary events in all the second step simulations was set equal to \( 2 \cdot 10^5 \), guaranteeing an estimation of \( e(t) \) values with relative statistical uncertainties below 0.3%.

The effective half-life \( T_{eff} \) of the left kidney was estimated by fitting the background-corrected energies deposited per event, \( e_{corr}(t) \), at the three time points, \( t = 2, 20 \) and 70 hrs. The \( e_{corr} \) were calculated as in Eq. (5). Additionally, the \( T_{eff} \) was estimated by fitting the energies deposited without background correction, \( e(t) \). Three time-point fits were obtained using all possible combinations of simulation outcomes performed at each time point, deducing the average effective half-life (\( T_{eff} \)) and its Standard Deviation SD\(_{MC} \), as described in the Supplementary Materials.

As anticipated, two kinds of kidney dosimetry procedures were performed: a complete image-based direct MC dosimetry for reference and a simplified dosimetry based on a single time-point MC dosimetry and on the external detector measurements proposed in this article.

In the complete direct MC dosimetry, the absorbed dose to the left kidney, \( D_{compl} \), was evaluated by integrating the mono-exponential fit function of the average dose rates \( \langle D(t) \rangle \) inside the left kidney VOI at the three time points of the SPECT/CTs, deduced from dose maps obtained from step 1) MC simulations (Section 2.3.1). Indicating with \( \langle D(t) \rangle \) the average absorbed dose in the left kidney VOI at time \( t \) in a simulation employing \( N(t) \) events in the first step, \( \langle D(t) \rangle \) was deduced as:

\[
\langle D(t) \rangle = \frac{\langle D(t) \rangle \cdot A(t)}{N(t)}
\]

where \( A(t) \) is total activity in the SPECT at time \( t \). \( D_{compl} \) was calculated analytically as follows:

\[
D_{compl} = D_0 \int_0^{\infty} e^{-\frac{t}{T_{compl}}} dt = \frac{D_0 \cdot T_{compl}}{\ln(2)}
\]

with \( T_{compl} \) and \( D_0 \) as fit parameters.

The simplified dosimetry was based on the assumption of selecting a single SPECT/CT at time \( T \), one of the three considered time points, and dose-rate-meter measurements on the patient at all three considered time points, to deduce the $^{17^7}$Lu effective half-life in the left kidney.

For \( T = 2, 20, 70 \) hrs, the kidney average dose \( D_{simpl,T} \) was evaluated from the average dose rate \( \langle D(t = T) \rangle \) and from the \( \langle T_{eff} \rangle \) deduced from the simulated probe measurements:

\[
D_{simpl,T} = \frac{\langle D(T) \rangle}{\langle T_{eff} \rangle} \int_0^{\infty} e^{-\frac{t}{\langle T_{eff} \rangle}} dt = \frac{\langle D(T) \rangle}{\langle T_{eff} \rangle} \frac{\ln(2)}{e^{\frac{T_{eff}}{\langle T_{eff} \rangle}}}
\]

3. Results

3.1. Experimental results of the phantom study

Table 5 details the effective half-lives obtained from the mono-exponential fits of the four acquired measurements, according to the procedure described in Sec. 2.1. The fits were done with the measurements in L-UP and L-DN positions, with and without the bottle resembling the intestines and with and without background correction. Standard errors (SE\(_{fit} \)) were evaluated according to the procedure detailed in Supplementary Materials. The CR measurements used to derive \( T_{eff} \) estimates lasted between 90 s (ER1) and 200 s (ER4).

The \( T_{eff} \) deduced from count rates without background correction differed <9% with respect to the expected value (54.9 hrs) set in the left kidney insert (Table 1) in the case including the intestines, and <4% in the case excluding the intestines. For \( T_{eff} \)’s deduced from background-corrected count rates, the differences compared to the reference dropped to below 2% in the case including intestines and below 3% excluding intestines. Therefore, the background correction improves the agreement between estimated and expected values, according to their uncertainties, irrespective of UP and DN position and intestine contribution. In general, background-uncorrected results tended to slightly overestimate the effective half-life, especially in the case including the intestines.

3.2. Simulation results from the phantom study

The average effective half-lives in the left kidney were deduced from Monte Carlo results both for $^{99m}$Tc and $^{17^7}$Lu sources simulated. Four time-point mono-exponential fit combinations, plus the three types of combinations of three time-point fits, were analysed according to the methodology described in Supplementary Materials. Results are reported in Table 6 and in Fig. 3.

The effective kidney half-lives obtained with MC simulating $^{99m}$Tc sources agreed within 2% with the expected value of Table 1 when using background-corrected energies deposited, while the agreement was
within 11% when using background-uncorrected results, without significant differences between the cases that included or excluded the intestines. This behaviour is in line with the results of the experimental measurements.

Comparing MC results with the corresponding experiment results listed in Table 5, the case with background correction including intestines agreed within 4%, the case without background correction including intestines within 5%, in the case with background correction excluding intestines within 3%, and the case without background correction excluding intestines within 8%.

For all the different cases examined no relevant differences emerged between the \( T_{\text{eff}} \)’s deduced from four time-point fits and the employed three time-point fits, while SD’s varied on the basis of the employed sample of time-points. MC results for \(^{99m}\text{Tc}\) using background-corrected energies deposited therefore agreed with both the expected value and the experimentally-derived values, according to their respective uncertainties, and irrespective of the presence of uptaking intestines.

Concerning \(^{177}\text{Lu}\), the agreement of \( T_{\text{eff}} \)’s with the expected value of Table 1 was within 4% using background-corrected results, within 7% using background-uncorrected results, irrespective of intestine contribution. The comparisons of \(^{177}\text{Lu}\) MC results with the experimental results shown in Table 5 found agreements in line (and even better concerning the background-uncorrected cases) with the comparison between \(^{99m}\text{Tc}\) MC results and Table 5. This evidence indicates the reliability of extending the count-rate method, experimentally tested on a phantom filled with \(^{99m}\text{Tc}\) nuclide, to \(^{177}\text{Lu}\), the radionuclide of interest for this study, without significant differences in accuracy.

### 3.3. Simulation results of the \(^{177}\text{Lu}\)-DOTATATE PRRT clinical case

Table 7 compares the effective half-life in the left kidney retrieved from complete image-based MC dosimetry, \( T_{\text{compl}} \), and the average effective half-life retrieved from the simulated probe measurement used for simplified dosimetry, \( \langle T_{\text{eff}} \rangle \), both defined in Sec. 2.3.2. Fig. 4b show a coronal slice of one of the dose rate maps deduced from simulations according to Sec. 2.3.1 and Eq. (6), and used in the calculation of \( T_{\text{compl}} \) and \( \langle T_{\text{eff}} \rangle \).

\[ T_{\text{compl}} \] and \( \langle T_{\text{eff}} \rangle \) deduced from background-corrected simulations agreed within 10%, which is, however, within the statistical uncertainties of the values. When comparing \( T_{\text{compl}} \) with the \( \langle T_{\text{eff}} \rangle \) deduced from the background-uncorrected simulation, the discrepancy rises to a value within 20%, something which falls outside of the statistical uncertainty intervals of the two compared values.

Fig. 5 shows the functions integrated to deduce the doses to the left kidney: the mono-exponential fit function of the three dose rate points, returning \( T_{\text{compl}} \) as fit parameter, in the case of complete MC dosimetry (Fig. 5a), and the analytical mono-exponential functions of Eq. (8), using \( \langle T_{\text{eff}} \rangle \) deduced from background-corrected results, for the simplified dosimetry, employing a single SPECT scan at 2 hrs (5b), 20 hrs (5c) or 70 hrs (5d).

Table 8 reports the values of the left kidney doses obtained with the complete MC dosimetry and simplified dosimetry procedures.

The doses obtained with the simplified procedure employing background-corrected results agreed within about 6%, 12% and 1% with respect to the result of the complete image-based procedure, respectively, if the single SPECT/CT scan employed for the calculation was performed at time \( T = 2, 20 \) and \( 70 \) h. In the case of the background-uncorrected results, the agreement between doses deduced with the simplified and complete method fell to within 23%, 10% and 4%, respectively, using the SPECT/CT scan performed at time \( T = 2, 20 \) and 70 h. The background-corrected results agreed more with the complete results with respect to the background-uncorrected ones for \( T = 2 \) and 70 hrs. The best agreement in terms of relative percent difference between dose average values was observed when using \( T = 70 \) hrs, taking in any case into account that each \( T_{\text{compl}} \) value has non negligible statistical uncertainty, which was within 14% for the doses deduced using background-corrected data.

### Discussion

In the frame of \(^{177}\text{Lu}\) PRRT, treatment optimization based on kidney dosimetry, by adjusting the cumulated therapeutic activity to maximize tumour absorbed dose while keeping renal radiation exposure to a safe level, has been successfully applied [3]. This approach is in line with the optimization principle stated in the EC Directive 2013/59/Euratom [7]. However, at present, only a minority of centres apply \(^{177}\text{Lu}\) treatment optimization based on personalized dosimetry information [8,9]. The costs of human resources, device occupation and other methodological aspects, such as quantitative accuracy and the complexity of the dosimetric procedures, are part of the arguments raised against the clinical routine implementation of personalized dosimetry in radionuclide therapy. In this context, simplified dosimetry methodologies are
welcome. The simplification of dosimetric procedures nevertheless must not result in insufficient accuracy and/or loss of personalization of the dosimetric assessments. Here we presented an original simplified methodology for the assessment of the absorbed dose in the kidneys applicable to patients being treated with $^{177}$Lu PRRT and/or PSMA. The proposed methodology enables the measure of patient-specific renal biokinetics; this can be achieved by means of multiple consecutive count-rate (or dose-rate) acquisitions from radioprotection instrumentation commonly available in nuclear medicine services.

Fig. 3. Box-plots of the left kidney estimated half-lives for phantom study MC simulations employing $^{99m}$Tc and $^{177}$Lu radionuclides, deduced from four-time-point fit combinations as explained in Section 2.2.2 and in the Supplementary Materials. In the two upper plots the results of fits done with count-rates corrected for the background, in the two lower plots with the fits done without background correction.

Fig. 4. a) Fusion of SPECT and CT coronal slices at $t = 2$ hrs, with blue circles indicating the L and M positions of the detector in the simulations (detector points at the body from the posterior side). b) Corresponding slice of dose rate map at 2 hrs, fused with CT, estimated with MC simulation. The contour of the left kidney VOI at 2 hrs used for organ dosimetry is represented in both a) and b), with light blue and white line, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 7

<table>
<thead>
<tr>
<th>probe signal</th>
<th>Dosimetry method</th>
<th>effective half-life (hrs)</th>
<th>statistical uncert. (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>background</td>
<td>Complete (3 SPECT/CT)</td>
<td>$T_{\text{compl}}$</td>
<td>45.08 $\pm$ 0.15</td>
</tr>
<tr>
<td>corrected</td>
<td>Simplified (1 SPECT/CT)</td>
<td>$T_{\text{simpl}}$</td>
<td>50 $\pm$ 3</td>
</tr>
<tr>
<td>background</td>
<td>Simplified (1 SPECT/CT)</td>
<td>$T_{\text{ct}}$</td>
<td>36 $\pm$ 3</td>
</tr>
<tr>
<td>corrected</td>
<td>+ 3 probe meas.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The simplification of dosimetric procedures nevertheless must not result in insufficient accuracy and/or loss of personalization of the dosimetric assessments.

Here we presented an original simplified methodology for the assessment of the absorbed dose in the kidneys applicable to patients being treated with $^{177}$Lu PRRT and/or PSMA. The proposed methodology enables the measure of patient-specific renal biokinetics; this can be achieved by means of multiple consecutive count-rate (or dose-rate) acquisitions from radioprotection instrumentation commonly available in nuclear medicine services.

In patient implementation, the obtained count-rate (or dose-rate) time curves can be thus employed in conjunction to a single time-point quantitative SPECT/CT to deduce the time evolution of the
absorbed dose-rates within kidneys and, consequently, their total absorbed doses.

This dosimetry workflow is a direct analogy with hybrid (planar plus a single quantitative SPECT) methods already presented in the literature [40]. In our case, the demand in terms of gamma camera occupation and use is reduced to only one SPECT/CT acquisition.

In a $^{99m}$Tc phantom experiment reproducing a simplified abdominal configuration of a patient (liver, kidneys inserts with an external intestine compartment), we tested the possibility of estimating the actual renal effective half-life from external count-rate measurements in the presence of radioactivity from organ compartments characterized by different half-lives. In this configuration, we obtained experimental estimates for the kidney $T_{\text{eff}}$ that reasonably agreed (within 3%) with the expected value, known from the experimental construction. We, furthermore, assessed the kidney $T_{\text{eff}}$ in two different positions (L-UP and L-DN), one 4-cm apart from the other, obtaining very comparable results; these results confirmed the robustness of the methodology against the particular positioning of the collimated external probe during the measurement. In this experimental configuration, we used the activity concentrations (and consequently total activities) present in the phantom compartments at different ER representatives of the respective quantities present in patients starting at 24 h and then up to one week after therapeutic administration. Indeed, we expect the proposed methodology to provide reliable information all along the measurement period required for appropriately fitting a mono-exponential function to then model the renal slow excretion phase. It is also important to note that the time required to obtain sufficient count statistics with the collimated external probe configuration used in our experiment was between 90 s (ER1) and 200 s (ER4), which is considerably shorter compared to the acquisition length typical for gamma camera imaging.

Our second step involved comparing the phantom experiment using MC simulation to replicate the experimental conditions. Additional MC

Table 8
Left kidney average absorbed doses $\langle D \rangle$, also expressed per unit of administered activity as $\langle D \rangle / A_{\text{adm}}$, evaluated with the complete and simplified dosimetry procedures, and the relative differences $\delta$ with respect to the complete dosimetry value.

<table>
<thead>
<tr>
<th>Probe signal</th>
<th>Dosimetry</th>
<th>SPECT/CT T (hrs)</th>
<th>$\langle D \rangle$ (Gy)</th>
<th>$\langle D \rangle / A_{\text{adm}}$ (Gy/GBq)</th>
<th>Stat. Uncert. on $\langle D \rangle$ (Gy)</th>
<th>$\delta$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>complete</td>
<td>2, 20, 70</td>
<td>3.700</td>
<td>0.66</td>
<td>0.006</td>
<td>/</td>
</tr>
<tr>
<td>/</td>
<td>simplified</td>
<td>2</td>
<td>3.94</td>
<td>0.71</td>
<td>0.54</td>
<td>+6.4</td>
</tr>
<tr>
<td>/</td>
<td>simplified</td>
<td>20</td>
<td>4.15</td>
<td>0.74</td>
<td>0.57</td>
<td>+12.1</td>
</tr>
<tr>
<td>/</td>
<td>simplified</td>
<td>70</td>
<td>3.66</td>
<td>0.66</td>
<td>0.51</td>
<td>-1.1</td>
</tr>
<tr>
<td>background corrected</td>
<td>simplified</td>
<td>2</td>
<td>2.87</td>
<td>0.51</td>
<td>0.23</td>
<td>-22.5</td>
</tr>
<tr>
<td>background corrected</td>
<td>simplified</td>
<td>20</td>
<td>3.33</td>
<td>0.60</td>
<td>0.27</td>
<td>-10.0</td>
</tr>
<tr>
<td>background corrected</td>
<td>simplified</td>
<td>70</td>
<td>3.84</td>
<td>0.69</td>
<td>0.31</td>
<td>+3.8</td>
</tr>
<tr>
<td>background uncorrected</td>
<td>simplified</td>
<td>2</td>
<td>2.87</td>
<td>0.51</td>
<td>0.23</td>
<td>-22.5</td>
</tr>
<tr>
<td>background uncorrected</td>
<td>simplified</td>
<td>20</td>
<td>3.33</td>
<td>0.60</td>
<td>0.27</td>
<td>-10.0</td>
</tr>
<tr>
<td>background uncorrected</td>
<td>simplified</td>
<td>70</td>
<td>3.84</td>
<td>0.69</td>
<td>0.31</td>
<td>+3.8</td>
</tr>
</tbody>
</table>

Fig. 5. In a) the red points are the $\langle \dot{D}(t) \rangle'$s, the solid blue line is the mono-exponential fit function integrated in Eq. (7) for the complete MC dosimetry. In b), c) and d) the single red point is the average dose rate evaluated at time $T = 2$, 20, and 70 hrs respectively, employed for the simplified dosimetry; the solid green line is the analytical mono-exponential function integrated in Eq. (8); the orange shaded region represents the absolute uncertainties on the function values; the dashed blue line is the same function represented as a solid blue line in a), plotted to compare complete and simplified dosimetry functions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
simulations were performed replacing the $^{99m}$Tc source used in the experimental setup with $^{177}$Lu, a radioisotope of interest for the therapeutic application. All MC simulations provided promising results for a possible application of the proposed methodology to a real patient case; in fact, all $T_{\text{eff}}$ estimates employing background-corrected data presented deviations within 4% of the expected values known from the experimental construction.

Indeed, in a third step we used sequential SPECT/CT data from a real patient to derive the renal effective time and absorbed dose estimates from a conventional 3D image-based dosimetry workflow. The obtained estimates were then compared with respective quantities obtained from MC simulations using the proposed simplified methodology, in which the patient data (patient geometry, tissue density and a single SPECT-derived quantitative activity concentration map) were input for use. Comparing the results from the three-SPECT dosimetry workflow with the proposed methodology presented different levels of agreement depending on the specific time point chosen for the quantitative SPECT/CT rescaling. The best agreement was obtained using SPECT data acquired at 70 hrs post administration (<2% difference between the two methods), and overall, the differences were <12%. Organ effective half-lives used in the phantom experiment and kidney absorbed doses obtained in the considered patient case example were in line with the published ranges of values [20,21].

The goal of the third step was to illustrate the applicability of the proof of concept previously presented in a phantom setup. Demonstrating the robustness of our methodology in patients will require extensive application and validation in a sufficiently large cohort of patients that is beyond the scope of the present work. Nevertheless, we believe that the promising results reported here will help pave the way to a clinical application of the proposed renal dosimetry methodology.

Something that emerged in both the phantom study and patient study was the benefit of also measuring between the kidneys, for a background estimation, and applying the background correction to the left kidney measurements, since the background-corrected measurements agreed more with the expected values in the determination of kidney effective half-life, and, for the patient case, also in the estimation of the average dose to the kidney.

There are a number of favourable aspects to highlight regarding our proposed dosimetry method. Multiple consecutive external acquisitions (using a collimated count-rate probe), as described in this work, should not represent a problem in a clinical application. The widespread availability and relatively low cost in terms of equipment and measurement time, not to mention the favourable impact in terms of patient comfort, make this method potentially achievable even for performing more than three time point measurements (typically between 24 hrs and 1 week post therapeutic activity administration [16,19,20,41]), therefore enabling a possible improvement in terms of the condition-keeping and accuracy of the $T_{\text{eff}}(\text{kidney})$ estimate on a full patient-specific bases.

It is worth noting that count-rate measurements can also be performed at the patient’s home by a trained technician or nurse if this is more convenient. This fact has particular relevance in the case that the patient, for any reason, cannot return to the hospital for late time point measurements (i.e., 1 week post therapy) that are considered key for a reliable dosimetry [16,20,41]. Minimal patient displacement is not only a benefit in terms of comfort but also when considering radiation protection that minimizes exposure of both the staff and the public.

The reproducibility of the measurement geometry should be carefully assessed. For this purpose, a mark could be drawn directly on the patient’s skin to enable a reproducible positioning and repositioning of the collimated probe. Identifying a favourable location should not be a problem though, since patients undergoing $^{177}$Lu therapeutic procedures are routinely given pre-treatment imaging that can be used on purpose with the help of morphological rendering available nowadays in most commercial SPECT/CT image reconstruction and analysis consoles. Otherwise, using ultrasound to identify the appropriate positioning would also be a non-ionizing imaging option.

Regarding the possible limitations of our proposed approach, the abdominal phantom employed was missing bone metastases and spleen compartments, and in the examined patient case there was normal spleen uptake and only moderate hepatic pathologic uptake.

However, the total activity present in the liver insert of the abdominal phantom (at least three times larger than the kidney total activity, as reported in Table 1) can be considered as an off-collimation tissue activity. This kind of activity did not affect the kidney half-life estimation, obtained by the collimated probe measurements.

We found that uptakes not located in the cone of view of the collimated probe, do not significatively affect kidney half-life estimation.

It can be argued that patients with an important tumour burden overlapping the collimated view across the kidney region might not be applicable to the proposed protocol. This aspect needs to be further investigated in clinical cases in future studies. Diagnostic pre-therapy imaging (such as $^{68}$Ga PET/CT DOTA or PSMA) could be considered for selecting patients who may or may not benefit from our proposed renal dosimetry method.

Finally, our study did not consider bone marrow and salivary gland dosimetry, which are relevant for the considered $^{177}$Lu therapeutic procedures; we only focused on simplified renal dosimetry. However, salivary gland dosimetry could, in principle, benefit from our proposed dosimetric approach because of their favourable anatomical location. Instead, bone marrow dosimetry could be performed in parallel to the proposed kidney dosimetry protocol, since it relies on blood sample measurements. In the case of a major bone metastases invasion, the cross-dose contribution from the disease should not be neglected; in this frame, future Monte Carlo developments could be of help.

Conclusions

The proposed simplified procedure to estimate the patient-specific kidney half-life in PRRT from external dose rate measurements was tested in an experimental phantom setup and successfully reproduced in a second step using MC simulations. We furthermore expanded our proof of concept by performing MC simulations on real patient data. The proposed workflow provided a satisfactory accuracy and would reduce the imaging required to derive the kidney absorbed dose to a unique quantitative SPECT/CT with benefits in terms of clinical workflows and patient comfort. Looking forward, specific studies are required to investigate the feasibility and reliability of the proposed methodology in a clinical implementation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jemp.2021.11.007.

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