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A Whole Body Dosimetry Protocol for Peptide-Receptor Radionuclide Therapy (PRRT): 2D Planar Image and Hybrid 2D+3D SPECT/CT Image Methods

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Corresponding Author:	M Dr. Belli
Corresponding Author's Institution:	
Corresponding Author E-Mail:	maria.belli@irst.emr.it
Order of Authors:	Maria Luisa Belli
	Emilio Mezzenga
	Valentina Di Iorio
	Monica Celli
	Paola Caroli
	Elisabeth Canali
	Federica Matteucci
	Elisa Tardelli
	Ilaria Grassi
	Maddalena Sansovini
	Silvia Nicolini
	Stefano Severi
	Marta Cremonesi
	Mahila Ferrari
	Giovanni Paganelli
	Anna Sarnelli
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TITLE:

A Whole Body Dosimetry Protocol for Peptide-Receptor Radionuclide Therapy (PRRT): 2D Planar Image and Hybrid 2D+3D SPECT/CT Image Methods

AUTHORS AND AFFILIATIONS:

Maria Luisa Belli[1], Emilio Mezzenga[1], Valentina Di Iorio[2], Monica Celli[3], Paola Caroli[3], Elisabeth Canali[3], Federica Matteucci[3], Elisa Tardelli[3], Ilaria Grassi[3], Maddalena Sansovini[3], Silvia Nicolini[3], Stefano Severi[3], Marta Cremonesi[4], Mahila Ferrari[4], Giovanni Paganelli[3], Anna Sarnelli[1]

[1]Medical Physics Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
[2]Oncology Pharmacy, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
[3]Nuclear Medicine Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
[4]Physics, IEO, European Institute of Oncology IRCCS, Milan, Italy

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Email addresses of co-authors:

Mezzenga Emilio (emilio.mezzenga@irst.emr.it)
Di Iorio Valentina (valentina.diiorio@irst.emr.it)
Celli Monica (monica.celli@irst.emr.it)
Caroli Paola (paola.caroli@irst.emr.it)
Canali Elisabeth (elisabeth.canali@irst.emr.it)
Matteucci Federica (federica.matteucci@irst.emr.it)
Tardelli Elisa (elisa.tardelli@irst.emr.it)
Grassi Ilaria (ilaria.grassi@irst.emr.it)
Sansovini Maddalena (maddalena.sasovini@irst.emr.it)
Nicolini Silvia (silvia.nicolini@irst.emr.it)
Severi Stefano (stefano.severi@irst.emr.it)
Cremonesi Marta (marta.cremonesi@ieo.it)
Ferrari Mahila (mahila.ferrari@ieo.it)
Paganelli Giorvanni (giovanni.paganelli@irst.emr.it)
Sarnelli Anna (anna.sarnelli@irst.emr.it)

Corresponding author:

Maria Luisa Belli (*maria.belli@irst.emr.it*)

SUMMARY

This method estimates the absorbed dose of different structures for peptide-receptor-radionuclide-therapy (PRRT) with the possibility of avoiding organ overlap on 2D-projections.

Serial whole-body planar images permit estimation of mean absorbed doses along the whole body, while the hybrid approach, combining planar images and 3D-SPECT/CT image, overcomes the limitations of structure overlapping.

ABSTRACT:

Peptide-receptor-radionuclide-therapy (PPRT) is a targeted therapy that combines a short-range energy radionuclide with a substrate with high specificity for cancer cell receptors. After injection, the radiotracer is distributed throughout the entire body, with a higher uptake in tissues where targeted receptors are overexpressed. The use of beta/gamma radionuclide emitters enables therapy imaging (beta-emission) and post-therapy imaging (gamma-emission) to be performed at the same time. Post-treatment sequential images permit absorbed dose calculation based on local uptake and wash-in/wash-out kinetics. We implemented a hybrid method that combines information derived from both 2D and 3D images. Serial whole-body images and blood samples are acquired to estimate the absorbed dose to different organs at risk and to lesions disseminated throughout the body. A single 3D-SPECT/CT image, limited to the abdominal region, overcomes projection overlap on planar images of different structures such as the intestines and kidneys. The hybrid 2D+3D-SPECT/CT method combines the effective half-life information derived from 2D planar images with the local uptake distribution derived from 3D images. We implemented this methodology to estimate the absorbed dose for patients undergoing PRRT with ^{177}Lu-PSMA-617. The methodology could, however, be implemented with other beta-gamma radiotracers. To date, 10 patients have been enrolled into the dosimetry study with ^{177}Lu-PSMA-617 combined with drug protectors for kidneys and salivary glands (mannitol and glutamate tablets, respectively). The median ratio between kidney uptake at 24 h evaluated on planar images and 3D-SPECT/CT is 0.45 (range:0.32-1.23). The comparison between hybrid and full 3D approach has been tested on one patient, resulting in a 1.6% underestimation with respect to full 3D (2D: 0.829 mGy/MBq, hybrid: 0.315 mGy/MBq, 3D: 0.320 mGy/MBq). Treatment safety has been confirmed, with a mean absorbed dose of 0.73 mGy/MBq (range:0.26-1.07) for kidneys, 0.56 mGy/MBq (0.33-2.63) for the parotid glands and 0.63 mGy/MBq (0.23-1.20) for submandibular glands, values in accordance with previously published data.

INTRODUCTION

Among peptide-receptor radionuclide therapies, ^{177}Lu-PSMA-617 PRRT combines a short-range beta emitter ^{177}Lu (1.9 mm maximum range in water, half-life 6.71 days) with a prostate-specific membrane antigen (PSMA) ligand. The overexpression of PSMA in 90-100% of local prostate cancer lesions and metastatic disease (lymph node and bone) is the key to this therapy. However, PSMA receptors are also expressed in different healthy tissues where high uptake is often observed during treatments. The main organs at risk are the kidneys, red marrow, and salivary and lacrimal glands, and the dose to these organs may reduce maximum injectable activity, impairing the therapeutic ratio.

Our institute (IRST IRCCS) activated a protocol with the aim of increasing the therapeutic ratio between lesions and healthy tissues, providing drug protectors combined with ^{177}Lu-PSMA-617 therapy. Mannitol, polyglutamate folate tablets combined with externally applied ice packs and

N-acetylaspartylglutammate acid eye drops are used for kidney and salivary and lacrimal gland preservation, respectively[1]. Post-infusion dosimetric studies are required to estimate the effective half-life (i.e., combination of physical and biological half-life) and absorbed dose for different structures of interest localized throughout the body (e.g., kidneys, salivary glands, disseminated lesions). This scenario requires whole body information obtained by acquiring sequential post-infusion whole-body planar images[2]. However, the overlap of high uptake structures (e.g., transient intestine uptake above the kidneys) requires 3D information capable of discriminating between different local uptakes that are blended on 2D projections. We implemented a hybrid method capable of providing a dosimetric evaluation of the entire body thanks to 2D planar images[2], maintaining 3D information on a selected region (e.g., abdominal region). This method combines the activity distribution provided by 3D SPECT/CT images with the effective half-life calculated from planar images. Information obtained from other non-overlapping structures (e.g., salivary glands) are derived from planar image study only. The blood sample method used for red marrow evaluation is described in another section.

The advantage of the hybrid approach is that the entire body can be scanned, whereas a full 3D SPECT/CT method limits cranio-caudal image extension, which may make it impossible to study structures that are distant from each other. However, the low image resolution of planar imaging and the need to implement an overlap correction using a single 3D SPECT/CT acquisition represent the main drawbacks.

In order to test the safety and efficacy of PRRT therapies, it is important to compare single institution data with data previously published by other groups. The majority of published data with ^{177}Lu-PSMA-617 are based on planar images. Thus, the described method could also be useful for the standardization of the methodologies used. Finally, it is worthy of note that the implementation of the methodology requires a high degree of collaboration between different professional figures involved (i.e., physicians, physicists, medical radiology technicians, nurses).

PROTOCOL:

The dosimetry procedure was performed according to the treatment protocol "Radiometabolic Therapy (RMT) with ^{177}Lu-PSMA-617 in advanced castration resistant prostate cancer (CRPC): efficacy and toxicity evaluation" (EUDRACT/RSO number: 2016-002732-32) **(Figure 1**). Selected patients underwent dosimetry evaluation based on performance status. All patients signed informed consent. Prior to treatment delivery, each patient underwent a ^{68}Ga-PSMA-11 PET/CT whole body scan.

NOTE: It is important to underline that some steps are linked specifically to the scanner used.

1. Pre-infusion imaging: transmission and blank image acquisition

NOTE: In this first image acquisition the patient's water equivalent thickness is evaluated. This value is used for attenuation correction of counts derived from 2D planar images acquired post ^{177}Lu-PSMA-617 injection.

1.1. Set low energy high resolution collimators (LEHR).

1.2. Open the image protocol acquisition on the workstation and select transmission scan whole body planar image acquisition.

1.3. Check the table velocity (e.g., 7 cm/min) and zoom (e.g., 1). Keep these values equal for the blank scan acquisition. Check that the option **Body Contour** is disabled.

1.4. Position the patient on the couch feet-first supine with arms at-rest along the side of the body. Use this position for all the images. If necessary, use available supports (arm support, knee wedge, pillow, blanket).

1.5. Take note of the exact position of the patient, using the scale number along the couch: vertex head position, knee position, foot position, couch height, all supports used. Take note of the patient's weight and height.

1.6. Set the SPECT dual heads at the opposite positions (i.e., 0° and 180°) and at the maximum distance from the FOV center. Raise the couch so that the patient is positioned at the FOV center and with head at the detector center.

1.7. Position the ^{57}Co flood support on the posterior camera and then the ^{57}Co flood itself on the support. Start image acquisition.

1.8. At the end of image acquisition, remove the ^{57}Co flood and support. Press **Unload** on the teach pendant. Help the patient to get up.

1.9. Repeat the image acquisition in the same way but without the patient positioned on the couch.

NOTE: Couch velocity, table height and camera distance should be set at the same value as the previous transmission image.

2. Post-infusion image acquisition: planar image

NOTE: Planar post-image acquisitions are used for effective half-life and mean absorbed dose evaluation of different structures.

2.1. Acquire first image 0.5-1 h after ^{177}Lu-PSMA-617 infusion (day 1, **Figure 1**).

2.1.1. **Acquire the first image before bladder voiding**. If the patient feels an urgent need for bladder voiding, provide a proper vessel for urine collection. Take care to include the vessel (or urine bag if the patient has a catheter) in the image.

2.2. Collect a 2 mL blood sample, close the collection tube and place it in a shielded box, noting the time.

2.3. Change to medium energy high resolution collimator (MEHR).

2.4. Open the image protocol acquisition on the workstation and select whole body planar image acquisition. Check the table velocity (e.g., 7 cm/min) and zoom (e.g., 1). Keep these values equal for all the other images. Check that the option **Body Contour** is disabled.

2.5. Position the patient on the couch, ensuring that the position is the same as that used for the previous image (i.e., pre-infusion transmission scan).

2.6. Set the SPECT dual heads at opposite positions (i.e., 0° and 180°). Raise the table so that the patient is positioned at the FOV center and with the head at the detector center.

2.7. Using the teach pendent, manually adjust the position of the posterior camera (i.e., positioned at 180°) to reach the minimum distance from the inferior couch profile.

2.8. Manually adjust the position of anterior camera (i.e., positioned at 0°) to reach minimum distance from the patient's profile. Take into account the entire body surface along the whole patient height to avoid collision during scanning.

2.9. Taking note of the position of the duel heads, start image acquisition.

2.10. At the end of image acquisition, press **Unload** on the teach pendant and help the patient to get up.

2.11. Repeat the same image acquisition with the same camera settings at 16-24 h (second image, day 2), 36-48 h (third image, day 3) and 120 h (fourth image, day 6) post infusion.

2.12. Collect a 2 mL blood sample at the same time as the SPECT image acquisition, close the collection tube and place it in a shielded box, making a note of the time.

3. Post-infusion image acquisition: 3D SPECT/CT

NOTE: On day 2 (16-24 h post infusion) a 3D image acquisition is performed, together with the planar image acquisition. The 3D SPECT/CT image focuses on the abdominal region and enables organ overlap (e.g., kidneys or intestinal loops) to be avoided on anterior/posterior projections.

3.1. After planar image acquisition, select the 3D SPECT/CT image inside the dosimetry protocol on the workstation.

3.2. Check that the proper image parameters have been set: acquisition modality (e.g., step-and-shoot), angle per projection (e.g., 5°), number of frames per rotation (e.g., 72), frame

duration (e.g., 3000 ms). Check that **Body Contour** is disabled.

3.3. Position the detector at the maximum distance from the center to avoid collision. Position the patient with arms lifted over the head. Position the patient table inside the camera until when the desired region is centered on the detector (e.g., kidneys and a specific lesion situated in the same region). Start image acquisition.

3.4. Acquire the corresponding CT image.

3.5. At the end of image acquisition, press **Unload** on the teach pendant and help the patient get up.

4. Image analysis

NOTE: Scatter, attenuation, and background corrections are implemented. Single organ and lesion mass are considered for absorbed dose evaluation. ROI and VOI are contoured on planar and 3D images.

4.1. Send all acquired images from the acquisition workstation to the analysis workstation.

4.2. For all post-infusion images, select emissive, low and high scatter images and click on the right panel of the dedicated workflow to create a scatter corrected image $2D_{SC}$, as follows:

$$2D_{SC} = 2D_{EM} - \left(\frac{2D_{SC1}}{W_{SC1}} + \frac{2D_{SC2}}{W_{SC2}}\right) * \frac{W_{EM}}{2}$$

where $2D_{EM}$, $2D_{SC1}$ and $2D_{SC2}$ are emissive, lower scatter and higher scatter 2D anterior or posterior planar whole-body images, respectively; W_{EM}, W_{SC1} and W_{SC2} are emissive, lower scatter and higher scatter energy window widths, respectively. Rotate posterior images.

4.3. Open each posterior image, click on **Image**, then **Reorient, Pan, Zoom...,** flag **Y mirror**, click **Apply & Quit**, and then save the rotated left-right image.

4.4. Open anterior and posterior (rotated) scatter-corrected planar images acquired on days 1, 2, 3 and 6 post infusion.

4.5. Select the image acquired on day 2 as the most suitable for ROI delineation. Contour organs: whole body (encompassing also urine vessel or bag when needed), kidneys, liver, spleen (if visible), parotid glands, submandibular glands. If possible, also contour some visible lesions. Contour the ROIs on the most useful image between anterior and posterior views (**Figure 2**). Contour a small ROI adjacent to each contoured structure for background.

4.6. Copy and paste all ROIs from the image acquired on day 2 to the anterior and posterior views of the other images (i.e., days 1, 3 and 6).

4.7. Use only ROI translation and do not modify to maintain the same organ dimension. In the event of an image with a high uptake region that overlaps with the delineated ROI (e.g., transient intestine uptake overlapped on kidney ROI), reduce single ROI to eliminate the problem[3]. For each image (i.e., days 1, 2, 3 and 6), select anterior image. Save contoured ROIs.

4.8. For each image, take note of average counts [c] and pixel dimension inside each ROI (including background ROIs) for both anterior and posterior views.

4.9. Open anterior transmission and blank scans, together with delineated ROIs. Copy and paste organ and lesions ROIs onto transmission scan. Adjust for organ mismatch, and if needed, enlarge or decrease organ contours for different image magnification.

4.10. For body attenuation, contour a structure encompassing head, shoulders, chest and abdomen, avoiding arms and legs (**Figure 3**).

4.11. Copy and paste all ROIs from transmission to blank scan.

4.12. Evaluate the water equivalent thickness *z* for each structure to estimate the self-attenuation. Take note of average counts inside each ROI on both transmission ($I_{transmission}$) transmission and blank (I_{blank}) scans. Calculate water equivalent thickness *z* as

$$z = \mu_{(57Co)} \times \ln\left(\frac{I_{transmission}}{I_{blank}}\right)$$

where $\mu_{(57Co)}$ is the attenuation coefficient for ^{57}Co flood previously measured with a uniform phantom.

4.13. Use the pre-treatment ^{68}Ga-PSMA-11 PET/CT scan. Contour organs on CT image: kidneys, liver, spleen, parotid glands and submandibular glands. Contour lesions on PET images. Assuming a uniform water composition for each structure, calculate the mass of each contoured structure using a unit density (1 g/mL).

4.14. Perform SPECT/CT image reconstruction, taking into account scatter correction, CT attenuation correction and resolution recovery. Set the same iterative reconstruction values as used for SPECT calibration (e.g., OSEM iteration and subset numbers, post reconstruction filtering).

5. Blood sample measurements

NOTE: Blood sample measurements are performed on High Purity Germanium (HPGe) detector for red marrow dose estimation.

5.1. Let blood sample decay for approximately 2 weeks to avoid detector saturation and high dead time.

5.2. After 2 weeks, measure one sample at a time. Because of the low activity, start measurements from the last acquired blood sample (i.e., from day 6).

5.3. Position the blood sample collection tube on the dedicated holder. Use the same geometry as that used for HPGe calibration. Position it on the HPGe detector and close the detector shielding case.

5.4. Open the software for spectrum acquisition and analysis. Check that the dead time is <3%. If higher, wait a few more days and perform the measurements then.

5.5. Select the proper HPGe calibration file corresponding to the 2 mL collection tube geometry holder. Start sample measurements (minimum 12 h measurements).

5.6. Analyze the spectrum by identifying the mean gamma peak and by calculating activity concentration. Take note of both measured sample activity and time and date measurements.

5.7. Repeat the same measurements and analysis for all of the blood samples.

6. Dosimetry evaluation

NOTE: The analysis is performed with a dedicated dosimetry software based on MIRD publications[4–8]. For each considered structure, effective half-life is evaluated on sequential 2D whole body images by bi- or mono-exponential curve fitting of time-activity curves. 3D SPECT/CT imaging is used to resolve the problem of high uptake intestine overlap on kidney structure by scaling the time-activity curves derived from planar images. Mean absorbed dose is then calculated for each structure mass. For red marrow dose evaluation, blood samples measurements are used and scaled to the patient's weight.

6.1. Planar images

6.1.1. For each image and structure, calculate the counts on anterior (I_A) and posterior (I_P) view as

$$I_{A,P} = \left(c_{ROI} - c_{bkgr}\right) * p$$

where c_{ROI} is the average count [c] for the considered ROI, c_{bkgr} is the average count [c] in the corresponding background region, and p is the pixel number inside the ROI.

6.1.2. For each ROI, calculate the uptake at each image time point as

$$A_{ROI} = \sqrt{\frac{I_A * I_P}{e^{-\mu_{(177Lu)} * z}}} * e^{\tau \times \Delta t}$$

where $\mu_{(177Lu)}$ is the attenuation correction factor for ^{177}Lu, τ is the ^{177}Lu physical half-life, Δt is the time difference between infusion and image acquisition[9], and z is the water equivalent

thickness evaluated on transmission scan.

6.1.3. Calculate the relative uptake as

$$\%IA_{2D} = \frac{A_{ROI}}{A_{WB1}} * 100$$

where $A_{WB1}$is A_{ROI} evaluated for whole body on the first post-infusion image. As whole urine is included in the image, this is considered as a reference for the total effective infused activity.

6.2. Hybrid 2D+3D SCPET/CT images

6.2.1. For SPECT/CT activity calibration, image a cylindrical phantom with a central sphere of known activity. Contour the central sphere VOI and calculate the calibration factor [cps/MBq] as

$$S = \frac{C}{t} * \frac{1}{A_k}$$

where *C* are the total counts inside the VOI [c], *t* the image acquisition time [sec] and A_k the known injected activity [MBq] inside the central sphere. SPECT/CT image for the patient is performed with the same acquisition and reconstruction parameter settings.

6.2.2. Open the SPECT/CT image. Contour volumes of interest (VOIs) (e.g., kidneys, visible lesion) are based on both uptake information and CT morphology. Calculate the activity in the structure as

$$A_{VOI} = \frac{C}{t} * S$$

6.2.3. Calculate

$$\%IA_{3D-24h} = \frac{A_{VOI}}{A_{inj}} * 100$$

where $\mathrm{A_{inj}}$ is the injected activity during treatment.

6.2.4. Calculate the scaling factor for the time activity curve as

$$F = \frac{\%IA_{3D-24h}}{\%IA_{2D-24h}}$$

where $\%IA_{2D-24h}$ is the $\%IA_{2D}$ calculated on planar image on day 2 (16-24 h) decay-corrected for physical half life at the time of injection.

6.2.5. Rescale the kidney 2D time activity curve $\%IA_{2D}$ with *F* factor accordingly. Perform dosimetry evaluation with OLINDA/EXM as described below.

6.3. Adult male phantom

6.3.1. Open dosimetry software. Select the radionuclide (e.g., ^{177}Lu) inside the **Nuclide Input**. Select the model (e.g., **Adult Male**) inside the **Model Input Form** module.

6.3.2. Go to the **Kinetic Input Form** module and click **Clear All Data**. Click on **Fit to Model** and a separate window will open.

6.3.3. In the **Time (Hr)** column, insert the hours post infusion for each image acquisition, in hour format (e.g., 1 h and 30 min will be 1.50). Scroll down the organ menu and select organs of interest (e.g., kidneys, liver, spleen).

6.3.4. For each organ, insert the relative uptake *%IA* at each image time point. Click **Refresh**.

6.3.5. For paired organs (i.e., kidneys) insert a single value as sum of left and right single relative uptakes *%IA*. Click Refresh and check the point distributions on the left-end side plot.

6.3.6. Perform a curve fitting using an exponential curve as

$$Activity(t) = Ae^{-at} + Be^{-bt} + Ce^{-ct}$$

A, B and *C* parameters may assume positive or negative values for wash-in and wash-out phase modeling, respectively. If data of time activity curves are decay-corrected, *a, b* and *c* parameters represent biological half life λ_{biol} and are all positive. Choose an appropriate curve-fitting model between mono, bi or tri-exponential curves. Flag the required parameters, insert starting values and click **Fit** until the fit is performed.

6.3.7. Take note of curve-fitting parameters. Calculate effective half-life as

$$eHL = \frac{\ln(2)}{\lambda_{phys} + \lambda_{biol}}$$

where λ_{phys} is the physical half life of ^{177}Lu, and λ_{biol} is the biological half life of ^{177}Lu-PSMA-617 compound. For λ_{biol}, consider the lowest values among *a*, *b* and *c* curve-fitting parameters (i.e., corresponding to the higher effective half life).

6.3.8. Repeat from step 6.3.3 to step 6.3.7. for each organ.

6.3.9. Insert the relative uptake at each image time point for the remainder of the body (namely **Total Body/Rem Body**) by subtracting the relative uptake of all considered organs from the whole-body uptake. Repeat from step 6.3.5 to step 6.3.7 for **Total Body/Rem Body**. Generally, a bi-exponential curve fitting is recommended.

6.3.10. Click **Done** and save the model. The program goes back to the **Kinetic Input Form** module and the number of disintegrations per unit of injected activity (namely *ND*, expressed in Bq*h/Bq) is visualized for each considered organ.

6.3.11. Go to **Main Input Form**. Click on **Doses**, and then **Modify Input Data**. In the box at the bottom **Multiply all masses by:**, insert the ratio between the patient's weight and Adult Male phantom weight (i.e., 73.7 kg). Click on the **Multiply all masses by:** button. All organ masses will be then rescaled accordingly. Insert single organ masses as calculated from CT delineation for the analyzed organs. For paired organs such as kidneys, insert the sum of left and right kidney masses. Click **Done**.

6.3.12. The report will display the mean absorbed dose normalized to injected activity, expressed in mGy/MBq. Take note of the total absorbed dose for considered organs (i.e., kidneys, liver, spleen, and Total Body).

6.3.13. Repeat for time activity curves derived from the hybrid 2D+3D SPECT/CT method.

6.4. Red marrow

6.4.1. Perform scaling for blood values to calculate Red Marrow dose.

6.4.2. Calculate the blood uptake at each blood sample acquisition as

$$A_{blood,2ml} = M * e^{\frac{\ln(2)*\Delta t}{\tau}}$$

where *M* is the activity measurement [MBq] obtained with HPGe 2 mL blood sample measurement.

6.4.3. Calculate the blood relative uptake $\%IA_{blood}$ as

$$\%IA_{blood} = \frac{A_{blood,2ml}}{A_{inj}} * \frac{2\ mL}{blood\ volume\ [ml]} * 100$$

where *blood volume* [mL] is the total blood volume estimation for the specific patient. This value is taken from the Adult Male standard phantom values[10].

6.4.4. Rescale to Red Marrow (RM) mass and calculate the RM relative uptake $\%IA_{RM}$ as

$$\%IA_{RM} = \%IA_{blood} * \frac{m_{RM}}{m_{blood}}$$

where $\frac{m_{RM}}{m_{blood}}$ is the ratio of standard Adult Male phantom of m_{RM} (Red Marrow mass) equal to 1120 g and m_{blood} (whole body blood mass) equal to 5000 g.

6.4.5. Go to **Kinetic Input Form** module and click **Clear All Data**. Click on **Fit to Model**. Scroll down the organ menu and select Red Marrow.

6.4.6. In the **Time (Hr)** column, insert the hours post infusion for each blood sample acquisition in hour format (i.e., 1 h and 30 min will be 1.50). Insert the values of $\%IA_{RM}$. Repeat steps 6.3.5-6.3.7. for Red Marrow.

6.4.7. Scroll down the organ menu and select Total Body/Rem Body. In the **Time (Hr)** column, insert the hours post infusion for each image acquisition in hour format (i.e., 1 h and 30 min will be 1.50). Insert the values of $\%IA_{Rem\,Body}$ equal to the difference between *%IA* of whole body calculated on planar images and $\%IA_{RM}$.

6.4.8. Repeat from step 6.3.5 to point for Red Marrow.

6.4.9. Click **Done** and save the Model.

NOTE: The program goes back to the **Kinetic Input Form** module and the number of disintegrations per unit of injected activity (namely *ND*, expressed in Bq*h/Bq) is visualized for each considered.

6.4.10. Go to **Main Input Form**. Click on **Doses**. Scale organ mass rescaling as the previous analysis on other organs.

6.5. Sphere model

6.5.1. Use a unit density sphere model for structures that are not available in the phantom (e.g., parotid and submandibular gland lesions).

6.5.2. For curve fitting, repeat from step 6.3.2 to step 6.3.10, substituting organ values with relative uptake for separated salivary glands and lesions.

6.5.3. Click **Done** and save the model.

6.5.4. The program goes back to the **Kinetic Input Form** module and the number of disintegrations per unit injected activity [Bq*h/Bq] is visualized for each considered organ. Take note of *ND* for each considered structure.

6.5.5. Go to **Model Input Form**. Click on **Spheres**.

6.5.6. For each structure, enter the calculated *ND.* Click on **Calculate Doses**. The report will display the mean absorbed dose normalized to injected activity, expressed in mGy/MBq, for discrete increasing sphere masses (g). Fit the curve with mono-exponential fitting and calculate the absorbed dose normalized to injected activity (mGy/MBq) for the specific structure mass.

6.5.7. For paired organs (e.g., salivary glands), perform the sphere model evaluation separately for left and right organs. Sum the mean absorbed dose for whole organ dose evaluation.

REPRESENTATIVE RESULTS:

Dosimetry was performed for 10 patients (7 undergoing first treatment cycle, 3 second cycle).

Four images after infusion were acquired for all patients, with the exception of patient no. 7 for whom it was not possible to acquire the last image at 120 h. Blood samples were acquired from all but 3 patients. One patient voided the bladder before the first post-infusion image acquisition. Injected activity was 5.5 GBq for 5 patients and 4.4 GBq for 5 patients.

With regard to curve fitting, mono or bi-exponential curve fitting was used for organ time-activity-curves. Bi-exponential curve fitting with wash-in and wash-out phases was used for salivary glands and a maximum uptake was observed around 16 h after infusion. For kidneys, combined wash-in/wash-out (5 patients) and pure wash-out (5 patients) phases were observed for kidneys. Bi- and mono-exponential fitting models were used. A pure wash-out phase was observed for whole body (bi-exponential), red marrow (bi-exponential) and liver (mono-exponential).

With regard to the 2D planar imaging method, median effective half-life was 30.4 h (range 12.2-80.6) for kidneys, 23.5 h (12.5-62.9) for liver, 31.6 h (25.6-60.7) for parotid glands, 31.0 h (5.3-61.0) for submandibular glands, 7.7 h (2.5-14.7) for red marrow and 51.1 h (31.6-79.7) for the whole body. With the 2D planar image method, median values of mean absorbed dose were 0.73 mGy/MBq (range 0.26-1.07) for kidneys, 0.12 mGy/MBq (0.05-0.53) for liver, 0.56 mGy/MBq (0.33-2.63) for parotid glands, 0.63 mGy/MBq (0.23-1.20) for submandibular glands, 0.04 mGy/MBq (0.02-0.07) for red marrow and 0.04 mGy/MBq (0.02-0.14) for the whole body.

The hybrid 2D+3D SPECT/CT method was used for kidney uptake evaluation. High intestinal uptake was observed from day 2 up to day 6, and largely overlapped the kidneys. The median ratio between kidney uptake at 24 h (day 2), evaluated on planar images ($\%IA_{2D-24h}$) and 3D SPECT/CT ($\%IA_{3D-24h}$), was 0.45 (range 0.32-1.23). For one patient, a full 3D SPECT/CT evaluation was also performed by acquiring both planar images and 3D SPECT/CT for all the days dedicated to the dosimetry (**Figure 4**). The time-activity curves derived from the three different methods were compared for left and right kidneys (**Figure 4**). The hybrid method assumes that the intestine overlap uptake correction observed on SPECT/CT acquired at 24 h was valid for all the other planar images acquired at different times. For this patient, the correction was valid for all time points for the right kidney (**Figure 4B**), whereas an underestimation of relative uptake was observed on day 1 for the left kidney (**Figure 4A**). Nevertheless, a discrepancy of only 1.6 % was observed between the hybrid and 2D methods in terms of mean absorbed dose of the hybrid method, with 0.320 mGy/MBq for the 3D method, 0.315 mGy/MBq for the hybrid method and 0.829 mGy/MBq for the 2D method.

FIGURE LEGENDS:

Figure 1. Image acquisition workflow for dosimetry evaluation. Main steps and timing of hybrid dosimetry procedure.

Figure 2. Sequential planar whole-body images (posterior projection) acquired at 1 h, 16-24 h, 36-48 h and 120 h post infusion. Delineated organs: kidneys, parotid glands, submandibular glands, lacrimal glands, liver, spleen, whole body, dorsal rachis lesion (red). Each delineated organ has a corresponding background region. This figure has been modified from Sarnelli et

al.[2].

Figure 3. Transmissive and blank anterior scan obtained with ^{57}Co flood. Delineated organs as described in **Figure 2**. This figure has been modified from Sarnelli et al.[2].

Figure 4. Comparison of 2D, hybrid 2D+3D, 3D SPECT/CT methods for transient intestine uptake overlap on kidneys. Time activity of left (**A**) and right (**B**) kidney curves (data refer to the same patient) derived using different methods: 2D whole body planar imaging (red line), hybrid 2D+3D SPECT/CT imaging (green line), full 3D SPECT/CT imaging (blue line). For the hybrid method, the time activity curve is rescaled on the basis of the image acquired 24 h post injection. The transient intestine uptake overlapping the kidneys is also shown on planar images (C). This figure has been modified from Sarnelli et al.[2].

DISCUSSION:

The method described enables whole body dosimetry to be performed for PRRT therapies and is a valid compromise between 2D whole-body and 3D dosimetry information in that it provides valuable information without significantly increasing image acquisition load. The method is also useful for the evaluation of the absorbed dose of overlapping structures and provides information on the structures lying outside the 3D SPCET/CT limited field of view.

The implementation of the methodology requires a high degree of collaboration between different subjects involved (i.e., physicians, physicists, medical radiology technicians, nurses) and is a time-consuming process in terms of image acquisition and post-processing analysis.

Our method could be further optimized. The number of image acquisitions could be reduced by avoiding the pre-injection transmission scan and evaluating the attenuation correction directly on whole-body CT or SCOUT images[11]. With regard to red marrow, as suggested by other authors[12], the absorbed dose could be evaluated on the basis of vertebra uptake rather than on blood samples. The contribution of bone lesions to the red marrow absorbed dose should also be taken into account.

A future application of the model will be the evaluation of dose-volume histogram (DVH) of structures imaged with the 3D SCPET/CT (e.g., kidneys, liver). The DVH provides more accurate information on dose evaluation than that of the mean absorbed dose and could be useful for comparisons with external beam radiotherapy dose constraints in terms of biological equivalent dose.

The method was developed for ^{177}Lu-PSMA-617 radiotracer but can also be used with other beta-gamma radiotracers.

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DISCLOSURES:

The authors have nothing to disclose.

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Figure 1

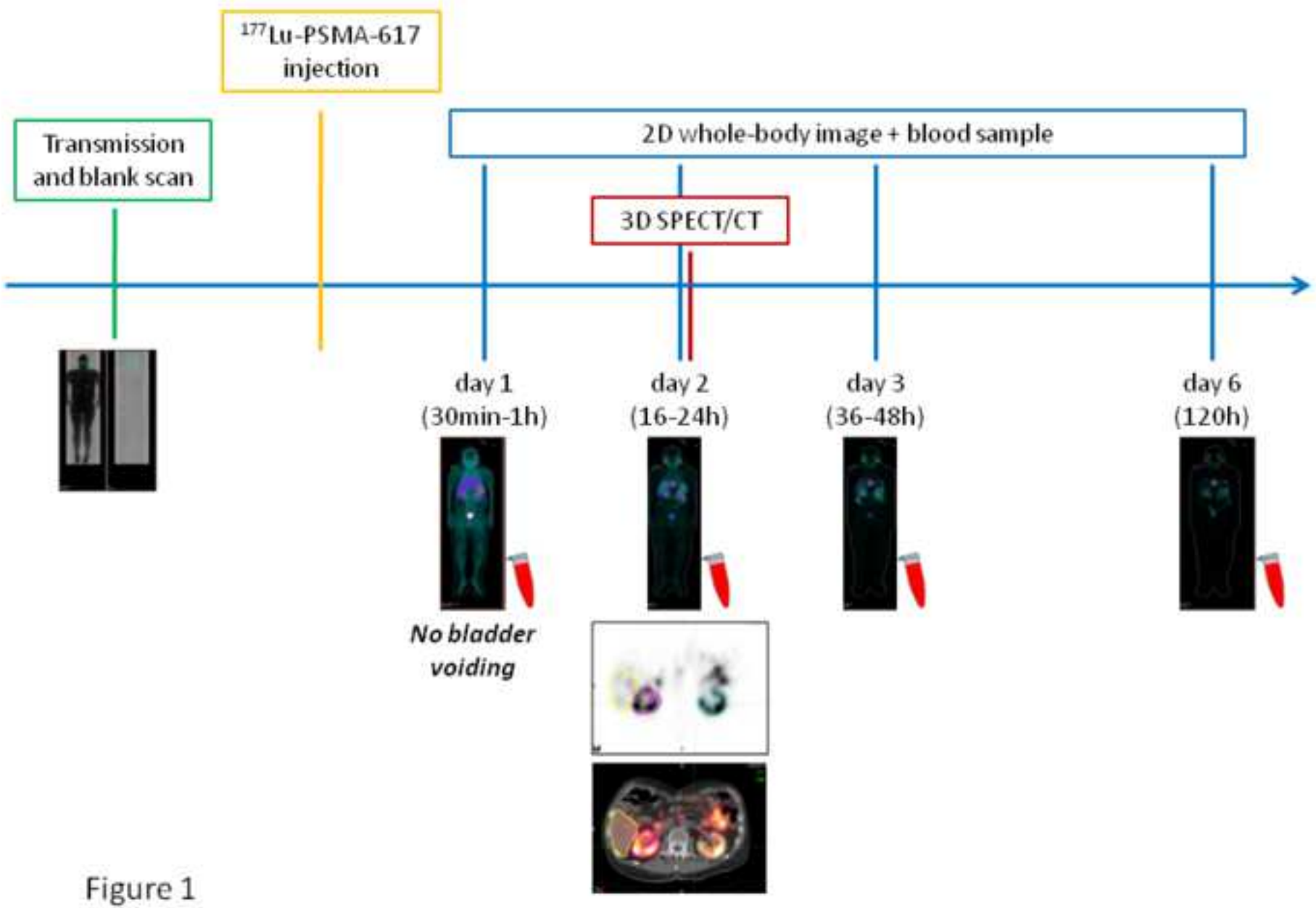

Figure 1

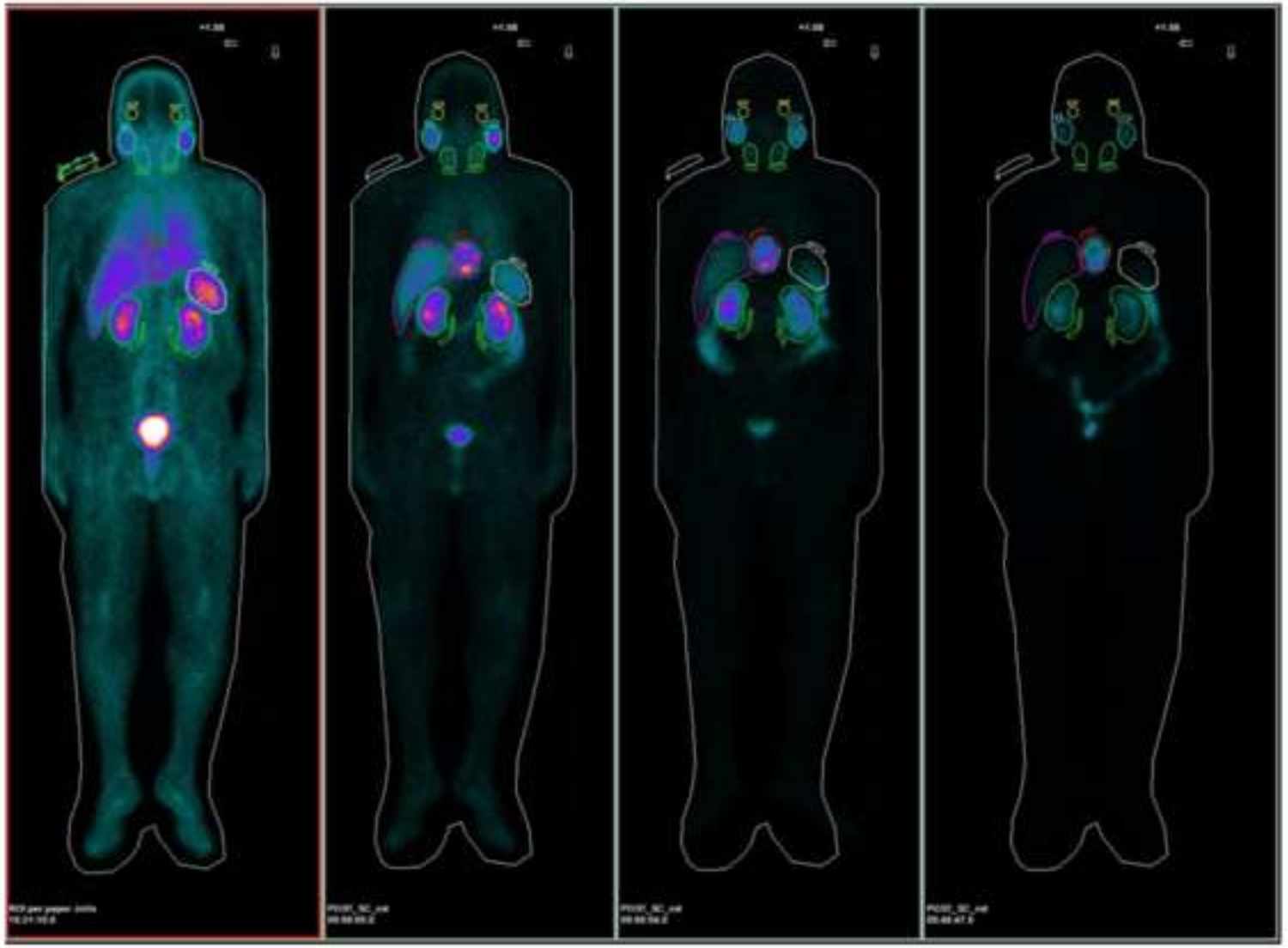

Figure 2

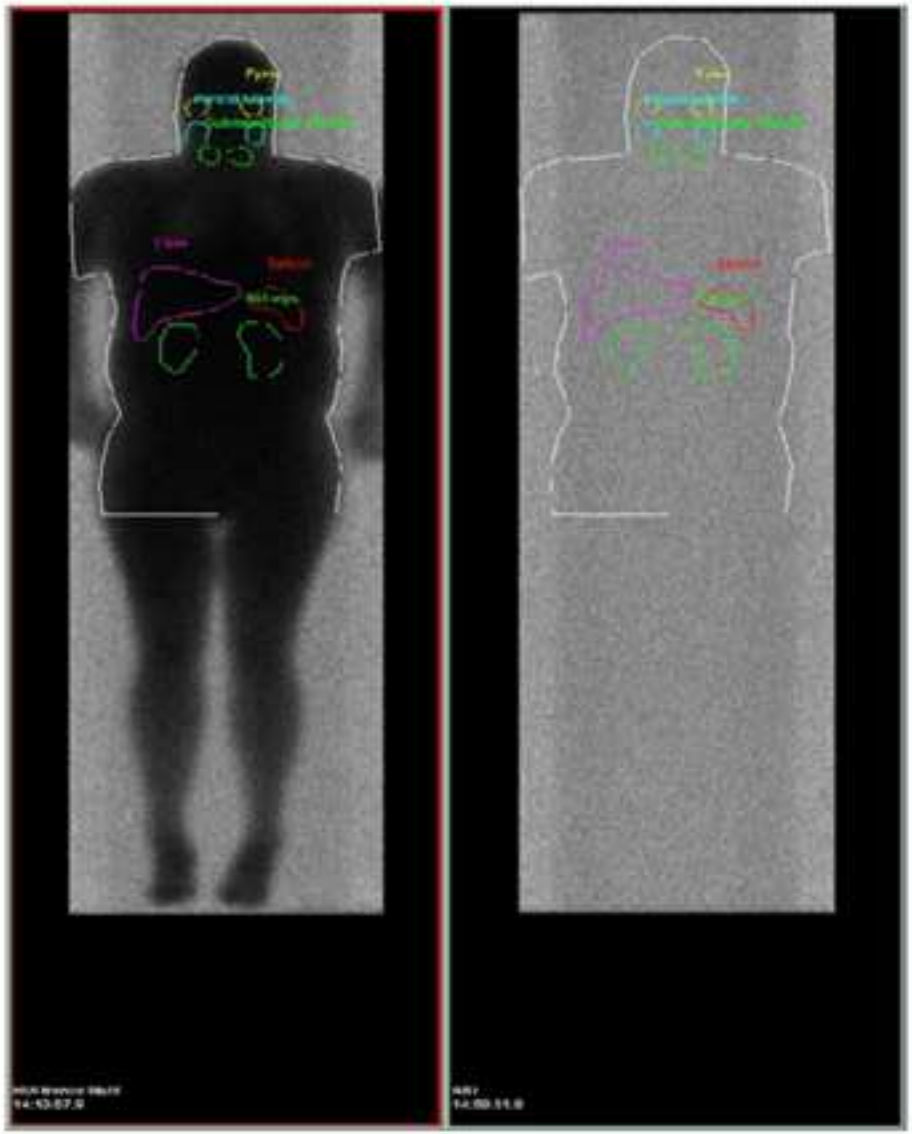

Figure 3

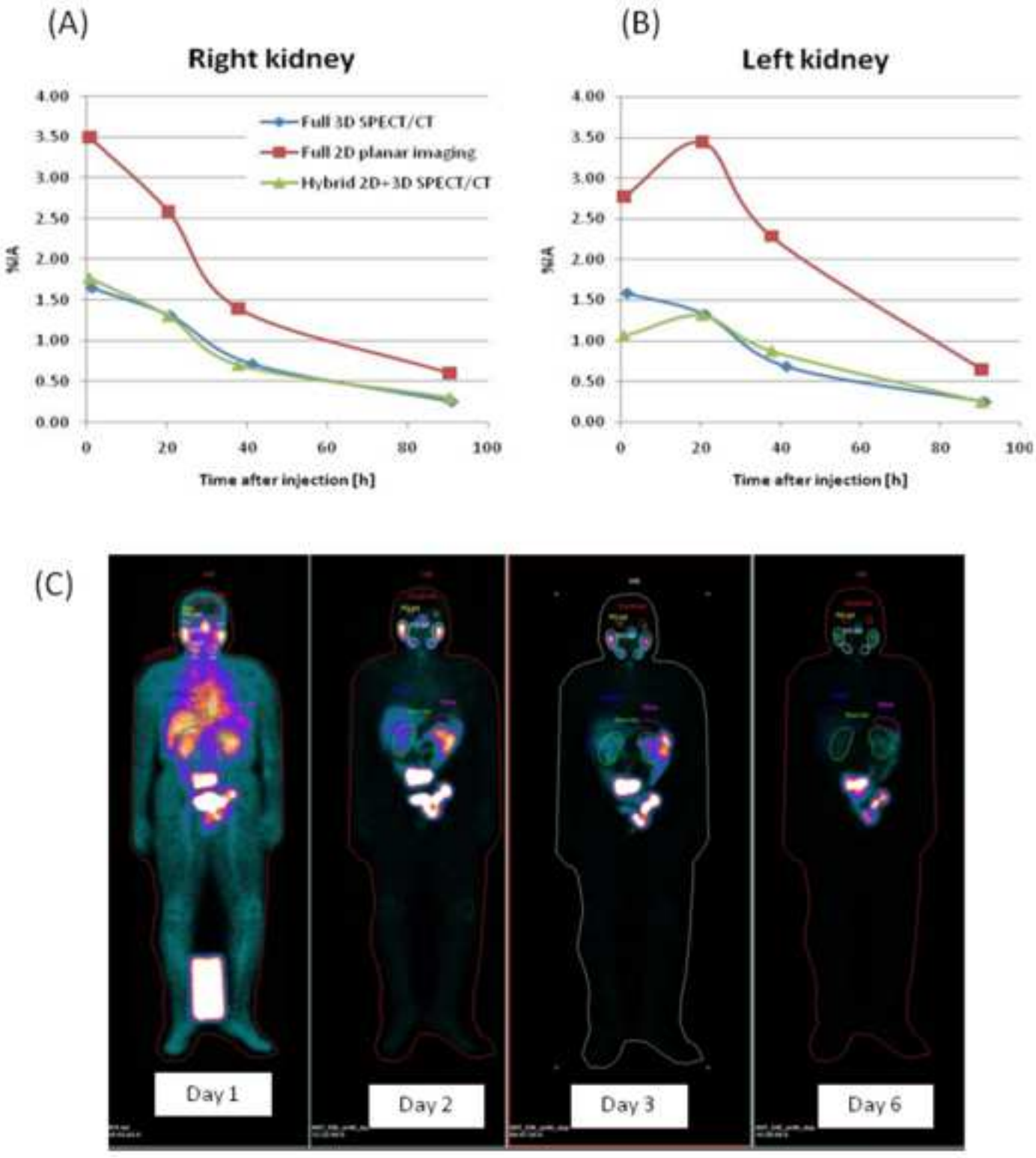

Figure 4

Name of Material/ Equipment

^{177}Lu EndolucinBeta

Biograph mCT Flow PET/CT

C-Thru ^{57}Co planar flood - Model MED3709
Cylindrical phantom with spheric insert

Discovery NM/CT 670 SPECT/CT

GalliaPharm ^{68}Ge/^{68}Ga Generator

GammaVision v 6.08

High Purity Germanium HPGe, model GEM30P4-70

MimVista Software

OLINDA/EXM v 1.1

PSMA 11

PSMA 617

Xeleris 4.0

Company

ITG - Isotopen Technologien München AG, Lichtenbergstrasse 1, 85748 Garching, Germany, info@itm.ag

Siemens Healthineers, Erlangen, Germany

Eckert & Ziegler, Strahlen- und Medizintechnik AG, Robert-Rössle-Str. 10, 13125 Berlin, Germany, info@ezag.de
Data Spectrum Corporation, 1605 East Club Boulevard, Durham NC 27704-3406, US, info@spect.com

International General Electric, General Electric Medical System, Haifa, Israel

Eckert & Ziegler, Strahlen- und Medizintechnik AG, Robert-Rössle-Str. 10, 13125 Berlin, Germany, info@ezag.de
Ortec, Ametek - Advanced Measurement Technology, 801 South Illinois Avenue, Oak Ridge, Tennessee 37830, US, ortec.info@ametek.com
Ortec, Ametek - Advanced Measurement Technology, 801 South Illinois Avenue, Oak Ridge, Tennessee 37830, US, ortec.info@ametek.com

MIM Software INC, Cleveland, OH 44122, US

RADAR - RAdiation Dose Assessment Resource, West End Ave, Nashville, TN 37235, US (now commercially available as OLINDA/EXM v 2.0, Hermes Medical
ABX advanced biochemical compounds - Biomedizinische,Heinrich-Gläser-Straße 10-14, 01454 Radeberg, Germania, info@abx.de

Endocyte Inc. (Headquarters), 3000 Kent Avenue, West Lafayette, IN 47906

International General Electric, General Electric Medical System, Haifa, Israel

Catalog Number	Comments/Description
	Radiotracer ^{177}Lu for therapy purpuse
	PET/CT scanner
	Calibration/planar source
	Phantom for SPECT/CT calibration
	SPECT/CT scanner
	^{68}Ge/^{68}Ga Generator of ^{68}Ga for imaging
	Gamma Spectorscopy software
	Gamma spectometer
	Workstation
	Dosimetry software
	Carrier for ^{68}Ga radiotracer
	Carrier for ^{177}Lu radiotracer
	Workstation

purpuse

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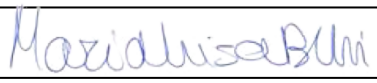
CORRESPONDING AUTHOR

Name:	Maria Luisa Belli
Department:	Medical Physics Unit,
Institution:	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola 47014, Italy
Title:	Physicist
Signature:	
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