Original paper

A dosimetry procedure for organs-at-risk in ^{177}Lu peptide receptor radionuclide therapy of patients with neuroendocrine tumours

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ABSTRACT

Purpose: Peptide receptor radionuclide therapy with ^{177}Lu -DOTATATE has become a standard treatment modality in neuroendocrine tumours (NETs). No consensus has yet been reached however regarding the absorbed dose threshold for lesion response, the absorbed dose limit to organs-at-risk, and the optimal fractionation and activity to be administered. This is partly due to a lack of uniform and comparable dosimetry protocols. The present article details the development of an organ-at-risk dosimetry procedure, which could be implemented and used routinely in a clinical context.

Methods: Forty-seven patients with NETs underwent ^{177}Lu -DOTATATE therapy. Three SPECT/CT images were acquired at 4, 24 and 144–192 h post-injection. Three blood samples were obtained together with the SPECT/CT acquisitions and 2 additional samples were obtained around 30 min and 1 h post-injection. A bi-exponential fit was used to compute the source organ time-integrated activity coefficients. Coefficients were introduced into OLINDA/EXM software to compute organ-at-risk absorbed doses. Median values for all patients were computed for absorbed dose coefficient D/A_0 and for late effective half-life $T_{1/2\text{eff}}$ for kidneys, spleen and red marrow.

Results: Dosimetry resulted in a median[interquartile range] of 0.78[0.35], 1.07[0.58] and 0.028[0.010] Gy/GBq for D/A_0 and of 55[9], 71[9] and 52[18] h for $T_{1/2\text{eff}}$ for kidneys, spleen and red marrow respectively.

Conclusions: A dosimetry procedure for organs-at-risk in ^{177}Lu -DOTATATE therapy based on serial SPECT/CT images and blood samples can be implemented routinely in a clinical context with limited patient burden. The results obtained were in accordance with those of other centres.

1. Introduction

Standardized dosimetry procedure is the cornerstone of molecular radiotherapy (MRT) individualization which, in turn, could bring improvements in therapeutic outcome [1]. Therapy individualization and outcome improvement rely on a complete determination of MRT therapeutic window—the range of absorbed doses which are effective without being harmful. Consequently, the knowledge of absorbed dose-

effect relationship is a key element to define organ-at-risk (OAR) absorbed dose safety limits and lesion response absorbed dose thresholds. To define this relationship, large datasets of standardized and reproducible inter-centre dosimetry results are mandatory.

Developing a standardized dosimetry procedure in MRT presents many challenges. The whole procedure can be described in a multi-step workflow: drug administration, data acquisition, activity quantification and absorbed dose computation (Fig. 1). At each step, different

Abbreviations: CE, Conformité Européenne; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; GMP, good manufacturing practice; MRI, magnetic resonance imaging; MRT, molecular radiotherapy; NET, neuroendocrine tumour; OLINDA/EXM, Organ Level Internal Dose Assessment/EXponential Modeling; OAR, organ-at-risk; PI, post-injection; PK, pharmacokinetic; SPECT, single photon emission computed tomography; TAC, time-activity curve; TIAC, time-integrated activity coefficient; VOI, volume of interest

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Fig. 1. Schematic representation of MRT dosimetry workflow.

parameters—such as patient burden, practicality, costs and, reproducibility and accuracy of the results obtained—are taken into account to guide clinical decisions. Though it is often overlooked, the standardization of the first step—drug administration—allows for the reproduction of therapies and the comparison of results across centres. Moreover, biological properties of the drug and physical properties of the radionuclide, which dictate the pharmacokinetic (PK) of the radiopharmaceutical as well as the OAR to consider, are key parameters in the determination of the scheduling and the type of medical data to be acquired (planar whole body scan, SPECT/CT, PET/CT, blood and/or urine samples...). In order to obtain reliable quantitative information from these medical data, precise and accurate calibration of the equipment is required to convert the number of counts measured into activity (Bq). The final step to consider is the computation of the absorbed dose to OAR and/or lesions which includes the definition of a time-activity curve (TAC), describing the evolution of the amount of activity in the considered source volumes over time.

In the specific context of ^{177}Lu peptide receptor radionuclide therapy (PRRT), each of the steps which are part of the dosimetry procedure has been studied separately over recent years. First, multiple phantom studies have been performed to assess and improve planar scintigraphy and SPECT imaging. Attenuation and scatter correction, contribution of Bremsstrahlung to the photopeak, partial volume effect and noise were addressed in order to improve OAR and lesion activity quantification [2–6]. Then to refine TAC fitting, different combinations of time-point measurements and mathematical models have been tested [7,8] and peptide kinetic models [9] or radiobiological models [10] have been implemented. Finally, organ- [11] and voxel-scale [12,13] dosimetry were developed based on Monte Carlo simulations to enhance computed absorbed dose accuracy. Dose inhomogeneities in tissue were also studied at the sub-millimetre level with Monte Carlo simulations [14].

In addition to these specific studies, dosimetry methods were developed for ^{177}Lu PRRT. They are based on blood [15–17] and/or urine [11,16,17] sampling completed with planar scintigraphy [15,17,18], SPECT/CT imaging [16,19] or a combination of both [20,21]. Yet, the proposed dosimetry procedures are seldom detailed. Furthermore, in contrast to external beam radiotherapy, very few end-to-end dosimetry softwares are available for MRT. Most are still under development and even those well-established are not yet CE certified or FDA approved.

This paper proposes and describes a dosimetry procedure for OAR in patients treated with ^{177}Lu -DOTATATE. Unlike many other dosimetry procedures, the one proposed here is entirely based on SPECT/CT images and blood samples acquired after the administration of ^{177}Lu -DOTATATE. For dosimetry purpose, SPECT/CT images present many advantages compared to planar images: organ anatomical volumes are accurately measured; radioactivity, in kidneys for instance, is quantified with minimal signal overlap from surrounding organs;

correction for background is no longer necessary. Blood sample activity measurements were used to evaluate red marrow self-absorbed dose. The available evidence suggests that there is no specific uptake in red marrow. Red marrow clearance and activity concentration are thus considered equal to that of blood [16]. To our knowledge, Svensson et al. [20] and Del Prete et al. [19] were the only authors so far to investigate SPECT and/or planar imaging to directly measure red marrow activity concentration. The latter underlined a slightly higher uptake in some patient's red marrow at 72 h compared to the uptake at 4 h PI. This observation might indicate a difference between blood and red marrow pharmacokinetics and should be systematically investigated in a future study.

Most of the decisions made during the development of the dosimetry method were required to address practical limitations as well as ethical requirements. The clinical dosimetry procedure was, in our experience, determined by consensus between medical physicists and nuclear medicine physicians. As a result, each of the potential solutions was not systematically investigated for each step of the dosimetry procedure. The rationale behind each decision was mostly based on literature, on practical criteria (such as the availability of staff, hardware and software) and on a good global understanding of the procedure. The resulting dosimetry procedure was implemented in clinical context and the obtained results were reported and compared to those from other centers obtained with other dosimetry procedures. This detailed description and discussion of our dosimetry procedure might help centers with limited time and resources to implement ^{177}Lu PRRT dosimetry.

2. Methods

2.1. Patient population

Forty-seven patients (20 women and 27 men; ranging from 43 to 83 years of age with a median age of 64) with neuroendocrine tumours (NETs) were evaluated in this study; 5 patients underwent splenectomy and 3 had a missing kidney. All patients had a high tumour uptake on the pre-therapeutic ^{68}Ga -DOTATATE PET/CT imaging (higher than the uptake of the physiological hepatic parenchyma), a documented disease progression (morphologically on a CT/MRI, or on the somatostatin receptor imaging, or alternatively progressing clinically with increase of a tumour marker (CgA or NSE or 5HIAA)), an adequate renal, liver and red marrow function and an ECOG performance status ≤ 1 . All patients underwent at least one ^{177}Lu -DOTATATE therapy cycle. OAR dosimetry was performed for each therapy cycle. The use of patient dosimetry data was authorized by the institutional Ethics Committee for the purpose of this study.

Fig. 2. VOI used for activity quantification on SPECT images for kidneys (a), spleen (b), liver (c) and remainder of the body (d), and organs' volume delineation on CT image (e).

2.2. ^{177}Lu -DOTATATE synthesis

The radiopharmaceutical ^{177}Lu -DOTATATE was produced within the radiopharmacy facility of the department of Nuclear Medicine at Institut Jules Bordet. Syntheses were performed by a fully automated process using the Modular-Lab PharmTracer (Eckert & Ziegler) with dedicated and validated Lutetium-peptide labelling GMP-compliant Cassettes (Eckert & Ziegler). ^{177}Lu -DOTATATE labelling was performed using 9 GBq of non-carrier added $^{177}\text{LuCl}_3$ in 0.04 mol/L HCl (ITG Isotope Technologies, Garching GmbH; ITM Isotopen Technologien München affiliate group, Garching, Germany) with 150 μg DOTATATE (Bachem AG) in a sodium ascorbate buffer (POLATOM) and heated for 20 min at 80 °C. The obtained raw radioactive solution was purified by solid phase extraction on a C18 cartridge (tC18 cartridge, Waters). The radiolabelled peptide was then eluted with 1 mL of 50% ethanol (Certa, Ph. Eur) in water (v/v), followed by 19 mL of saline (B. Braun), with a sterile filtration as a final step (0.22 μm Millex GV, Millipore). After quality controls were performed and the acceptance criteria were met, ^{177}Lu -DOTATATE was released for patient administration.

2.3. ^{177}Lu -DOTATATE administration

Before ^{177}Lu -DOTATATE administration, 8 mg ondansetron, 40 mg methylprednisolone and 20 mg metoclopramide were given in a 200 mL perfusion to prevent nausea or vomiting. Thirty minutes later, a 4–6 h infusion of amino acid solution (Proteinsteryl Hepa 8%, 2 L, Fresenius Kabi) was started for nephroprotection. Thirty to 50 min later, a slow ^{177}Lu -DOTATATE intravenous injection was started lasting 10–20 min. The ^{177}Lu -DOTATATE prescribed activity was 7.4 GBq, however activities were sometimes reduced by half for safety reasons (e.g. previous myelotoxicity). The ^{177}Lu -DOTATATE prepared activity was measured before and after the injection in a radionuclide calibrator (CRC-15R, Capintec; manufactured in 1990) calibrated for ^{177}Lu activity measurement [22]. The residual activity was subtracted to compute the net administered activity.

2.4. Data acquisition

After each injection of ^{177}Lu -DOTATATE, patient SPECT/CT images were planned at 4, 24 and 168 h post-injection (PI) on a SPECT/CT camera (Symbia TruePoint T, Siemens Healthcare; manufactured in 2008). Three blood samples were taken together with SPECT/CT acquisitions and 2 additional samples were planned at 0.5 and 1 h after the end of each ^{177}Lu -DOTATATE injection. Exact start and end times of injection along with exact acquisition and sampling times were reported.

The SPECT/CT field of view covered the upper abdomen including kidneys, liver and spleen (one bed position). Acquisitions were performed with a parallel-hole “medium energy low penetration” collimator in non-circular (auto-contour) step-and-shoot mode with 32 frames (180°) of 40 s per head. Acquisition time was doubled for the late time-point measurement to compensate for the low counting statistics. The main photopeak energy window was centred on 208 keV photopeak (20% width) and was combined with a contiguous lower window (10% of main energy peak in width) for scatter correction with dual energy window method. SPECT images were reconstructed using

OSEM algorithm from the camera manufacturer (Syngo MI Applications version 8.5. Siemens Healthcare: 128 × 128 matrix, 16 iterations, 16 subsets, Gaussian post-filtering of 12 mm at full width at half maximum, scatter correction, attenuation correction and collimator depth-dependent three-dimensional resolution recovery).

The acquisition and reconstruction parameters, and a calibration method (to convert count into becquerel) had to be developed for SPECT/CT images. Specific measurement settings and quality control techniques were also developed for blood sample measurement in NaI (TI) well counter. These procedures were a trade-off between patient comfort and clinical feasibility on the one hand, and measurement accuracy and reproducibility on the other hand; they were further detailed in a previous publication [22].

2.5. ^{177}Lu -DOTATATE activity quantification in source volumes

^{177}Lu -DOTATATE activity was quantified in kidneys, spleen, liver, red marrow and remainder of the body—whole body minus kidneys, spleen, liver and red marrow. The total activity in each volume was obtained by multiplying the anatomical volume by the mean activity concentration. PMOD v3.4 software was used to measure volumes and activity concentrations on patient SPECT/CT images (Fig. 2).

Kidneys, spleen and liver anatomical volumes were manually outlined on the CT of the first SPECT/CT acquisition for each therapy cycle. Kidney volume included renal cortex and medulla, and excluded renal pelvis. Red marrow mass, as defined by Stabin et al. [23] in standard man and woman phantoms, was adapted to the patient's height as follows [24]:

$$m_{\text{BM patient}} = m_{\text{BM phantom}} \times \frac{TBH_{\text{patient}}}{TBH_{\text{phantom}}}$$

where $m_{\text{BM patient}}$ and $m_{\text{BM phantom}}$ are the bone marrow masses of the patient and the standard phantom respectively, and TBH_{patient} and TBH_{phantom} are the total body height of the patient and the phantom respectively. A general soft tissue density of 1.04 g/cm³ [25] was used to convert red marrow mass into volume and patient weight into patient volume for the remainder of the body. Then kidney, spleen, liver and red marrow volumes were subtracted from the patient whole body volume to obtain the volume of the remainder of the body.

Activity concentrations in kidneys, spleen, liver and remainder of the body were measured on the 3 SPECT images of each therapy cycle. As depicted on Fig. 2a and b, 3 spherical volumes-of-interest (VOIs) (4 cm³) were placed in healthy tissue in both kidneys and in the spleen. As liver and hepatic metastases were considered as a unique source organ, the total activity in combined liver and lesions was measured by drawing a single liver volume (Fig. 2c). This volume was larger than anatomic boundaries to take into account partial volume effect. The activity concentration in the remainder of the body was sampled with 2 large VOIs placed in the gluteal region (Fig. 2d).

Raw measurements on SPECT images (C_{mes} expressed in counts/voxel) were converted into activity concentrations (A_{mes} expressed in MBq/mL) as follows [22]:

$$A_{\text{mes}} = \frac{C_{\text{mes}}}{T_{\text{acq}} \times CF}$$

With T_{acq} the acquisition duration (i.e., time per frame multiplied by total number of frames; $T_{acq} = 40 \text{ s} \times 32 \text{ frames} \times 2 \text{ heads}$), and CF the conversion factor for the considered situation ($CF = 1.09 \text{ (cps/voxel)/(MBq/mL)}$).

On the assumption that there is no specific red marrow uptake, red marrow clearance and activity concentration were considered equal to those of blood. Red marrow activity concentration was therefore measured in 5 blood samples for each therapy cycle. Out of those, three 200 μL samples were taken and measured in a NaI(Tl) well counter (2480 WIZARD², Perkin Elmer; manufactured in 2011) for 20 min each. Activity quantification was made by summing the number of counts detected in a 20% energy window centred on 208 keV photopeak. Raw measured data (expressed in counts/mL) were divided by the acquisition duration ($T_{acq} = 1200 \text{ s}$) and converted into kBq/mL with the conversion factor for the considered situation ($CF = 31.5 \text{ cps/kBq}$) [22].

2.6. Absorbed dose computation to OAR

Absorbed dose delivered to OAR was computed using the absorbed fraction method, well known as the MIRD schema [26,27].

The time-integrated activity coefficient (TIAC) for a given source volume is computed by integrating the TAC. In this work, the equation used to describe the evolution of activity in kidneys, spleen and liver over time is the difference between two decreasing exponentials (Fig. 3a):

$$A_{1-2}(t) = A_1(0) \times \left(\exp\left(-\frac{\ln 2}{T_{1/2\text{eff1}}} \times t\right) - \exp\left(-\frac{\ln 2}{T_{1/2\text{eff2}}} \times t\right) \right)$$

With $T_{1/2\text{eff1}} > T_{1/2\text{eff2}}$.

The equation used to describe the evolution of the activity in the remainder of the body and in the blood over time is the sum of two decreasing exponentials (Fig. 3b):

$$A_{3+4}(t) = A_3(0) \times \exp\left(-\frac{\ln 2}{T_{1/2\text{eff3}}} \times t\right) + A_4(0) \times \exp\left(-\frac{\ln 2}{T_{1/2\text{eff4}}} \times t\right)$$

With $T_{1/2\text{eff3}} < T_{1/2\text{eff4}}$ and $A_{3+4}(0) = A_3(0) + A_4(0)$

And with:

- t , the time elapsed between the beginning of the administration and the considered point;
- $A_n(t)$, the fraction of injected activity at time t ;
- $T_{1/2\text{eff1}}$ and $T_{1/2\text{eff4}}$, the bi-exponential late effective half-lives;
- $T_{1/2\text{eff2}}$ and $T_{1/2\text{eff3}}$, the bi-exponential early effective half-lives.

Bi-exponential functions were computed with a free and open-source software for numerical computation (Scilab 5.5.1). The Levenberg-Marquardt algorithm implemented in Scilab (lsqr solve function) was used to fit the model function to data using non-linear least squares. By definition, the fraction of injected activity in $t = 0$ (e.g. beginning of ¹⁷⁷Lu-DOTATATE administration) was $A_{1-2}(0) = 0$ for kidneys, spleen and liver and $A_{3+4}(0) = 1$ for the remainder of the body. $A_{3+4}(0)$ for the red marrow was defined by the bi-exponential fit. The curves obtained were the TACs of the considered source volumes and they were integrated from $t = 0$ to $t = \infty$ to obtain the TIACs.

The OLINDA/EXM software version 1.0 (Organ Level Internal Dose Assessment/EXponential Modeling) [28] was then used to compute absorbed doses. The computed TIACs were introduced in the OLINDA/EXM software for kidneys, spleen, liver, red marrow and remainder of the body. Absorbed dose coefficients were scaled by adjusting the phantom masses according to patient anatomy [29]. As the OLINDA/EXM software makes no distinction between right and left kidneys, their masses and TIACs were summed.

$$A_{1-2}(t) = A_1(0) \times \left(\exp\left(-\frac{\ln 2}{T_{1/2\text{eff1}}} \times t\right) - \exp\left(-\frac{\ln 2}{T_{1/2\text{eff2}}} \times t\right) \right)$$

$$A_{3+4}(t) = A_3(0) \times \exp\left(-\frac{\ln 2}{T_{1/2\text{eff3}}} \times t\right) + A_4(0) \times \exp\left(-\frac{\ln 2}{T_{1/2\text{eff4}}} \times t\right)$$

Fig. 3. Bi-exponential fits and equations used to describe the evolution of activity over time in (a) kidneys, spleen and liver, and (b) red marrow and remainder of the body, the time elapsed between the beginning of the administration and the considered point; $A_n(t)$, the fraction of injected activity at time t ; $T_{1/2\text{eff1}}$ and $T_{1/2\text{eff4}}$, the bi-exponential late effective half-lives; $T_{1/2\text{eff2}}$ and $T_{1/2\text{eff3}}$, the bi-exponential early effective half-lives. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Statistics

Descriptive statistics are presented as median[interquartile range]. The late effective half-life $T_{1/2\text{eff}}$ and the absorbed dose coefficient D/A_0 are presented in box-and-whisker plots for kidneys, spleen and red marrow. Points outside the whiskers are mild outliers defined as values outside the range $[Q1 - 1.5 \times IQR; Q3 + 1.5 \times IQR]$ with $Q1$ and $Q3$ the first and third quartiles.

Time and activity at the bi-exponential maximum or inflection point, volume, $T_{1/2\text{eff}}$, and TIAC are presented in supplementary data for kidneys, spleen, liver, red marrow and the remainder of the body (Table 2).

4. Results

The computed net administered activity of ¹⁷⁷Lu-DOTATATE was 7.39[0.19] GBq for 43 patients and 3.78[0.07] GBq for 4 patients who were prescribed halved activities. Dosimetry resulted in D/A_0 equal to 0.78[0.35], 1.07[0.58] and 0.028[0.010] Gy/GBq for kidneys, spleen and red marrow respectively (Fig. 4). The bi-exponential PK fitting

Fig. 4. Box-and-whisker plots of absorbed dose coefficient for kidneys, spleen and red marrow during first ^{177}Lu -DOTATATE therapy cycle of 47 patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

resulted in the following $T_{1/2\text{eff}}$: 55[9], 55[9], 71[9] and 52[18] h for right kidney, left kidney, spleen and red marrow respectively (Fig. 5).

5. Discussion

During the last decades, many publications have reported on ^{177}Lu PRRT efficacy [30,31] as well as renal and haematological toxicity [17,32,33]. However, no consensus has been reached regarding absorbed dose threshold for lesion response, absorbed dose limit to OAR, optimal fractionation and activities to be administered. This has been partly due to the lack of uniform and comparable dosimetry protocols possibly supported by adequate end-to-end dosimetry software.

In this article, we proposed a specific procedure for the dosimetry of OAR in the context of ^{177}Lu PRRT of patients with NETs. The method consisted in the acquisition of 3 SPECT/CT images at 4, 24 and 144–192 h PI and 5 blood samples (of which 3 were obtained together with the SPECT/CT acquisitions and 2 were obtained around 0.5 and 1 h after ^{177}Lu -DOTATATE administration). A bi-exponential fit was used to compute the irradiation source volume TIAC which were subsequently introduced into OLINDA/EXM software for OAR absorbed dose assessment.

In our institution, according to Belgian national regulation, patients are discharged when their dose rate at 1 m is less than $20 \mu\text{Sv/h}$. For the considered patient cohort, this threshold was systematically reached not later than 24 h after therapeutic administration. This fact facilitates the image and blood sample acquisitions during the first 24 h after therapeutic administration.

For practical reasons, blood samples were collected simultaneously with SPECT/CT images at 4, 24 and 168 h after administration. Two additional samples were collected during the first hour following ^{177}Lu -DOTATATE administration. This decision was taken to better objectify the fast drug clearance from blood. As patients might be nauseous due to the administration of amino acids, we chose to wait for 4 h for early SPECT/CT. A second SPECT/CT was performed before the patient left the hospital. As a late imaging point was essential, an additional SPECT/CT was obtained 7 days later. These considerations were further supported by Guerriero et al. [7] who have highlighted the significance of the choice of the time-point measurements on the upcoming dosimetry results. They have clearly shown that a late measuring point, after two radionuclide effective half-lives (i.e. approximately 2×50 h for ^{177}Lu -DOTATATE), was essential to avoid differences up to 70% between fitting methods. They also reported that considering only time-point measurements after 24 h could lead to significant over- or under-estimations depending on the fitting method used. According to these recommendations, most groups (Table 1) make use of an early imaging point before 24 h and a later one 7 days after the administration; other time-point measurements are scheduled at 24, 48 or 72 h.

The MIRD pamphlet No. 23 [34] reports that the number of time-point measurements depends on the number of exponential terms in the TAC of each source volume and their scheduling depends on the clearance rate for each exponential term. It is further reported that at least three time-point measurements should be taken for each exponential term involved. As acquiring more than 3 or 4 imaging time-points was burdensome for patients, most authors preferred trapezoidal or mono-exponential TAC fittings (Table 1). However, Guerriero et al. [7] have shown that, when data were available before 24 h, a bi-exponential fitting was recommended and more reproducible. Thus, despite our lack of time-point measurements, we considered that the evolution of activity in organs over time was better described by a bi-exponential equation.

As the activity measured on SPECT images is a combination of both the activity in organs' cells and in the blood circulating in the organ, both PKs were considered in kidneys, spleen and liver TAC fitting. For these organs, the evolution of activity over time was described by the difference between two decreasing exponentials resulting in a two phase TAC. The first phase of the TAC (i.e. until 5–10 h PI) increases rapidly and the second phase decreases more slowly. Basically, the first phase of the TAC is thought to coincide with the massive specific binding of ^{177}Lu -DOTATATE on cells in organs and tumours. The second phase of the TAC corresponds to the renal plasma clearance and the ^{177}Lu physical decay which overwhelm the residual specific binding of ^{177}Lu -DOTATATE on cells in organs and lesions.

Fig. 5. Box-and-whisker plot of late effective half-life for kidneys, spleen and red marrow during first ^{177}Lu -DOTATATE therapy cycle of 47 patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Summary of dosimetry procedures used in different centres and corresponding dosimetry results obtained for different target volumes (* expressed as mean $\pm$ SD or [Q1; median; Q3]).

	Author	Planar images	SPECT/CT	Blood samples	Urine samples	Fit function	Dose computation	Number of patients	d * [Gy/GBq]	T _{1/2eff} * [h]
Kidneys	Bergsma et al. [42]	24, 72–96, 168 h PI	/	/	/	mono-exponential	self-dose	407	0.67 $\pm$ 0.20	[27; 58; 135]
	Del Prete et al. [19]	/	4, 24, 72 h PI	/	/	trapezoidal + mono-exponential	OLINDA/EXM	36	0.55 $\pm$ 0.2	(NA)
	Garkavij et al. [18]	0.5, 24, 96, 168 h PI	/	/	/	trapezoidal + mono-exponential	OLINDA/EXM	21	1.15 $\pm$ 0.29	(NA)
	Sandström et al. [11]	24, 96, 168 h PI	24, 96, 168 h PI	0.5, 1.0, 2.5, 4, 8, 24 h PI	first 24 h	mono-exponential	self-dose	200	[0.47; 0.61; 0.73]	(NA)
	Sundlöf et al. [21]	1, 24, 48 or 96, 168 h PI	24 h PI	/	/	trapezoidal + mono-exponential	self- and cross-dose	51	[0.3; 0.61; 1.98]	[38; 52; 69]
	Svensson et al. [43]	2, 24, 48, 168 h PI	24 h PI	/	/	mono-exponential	self-dose	51	0.63 $\pm$ 0.2	(NA)
	Wehrmann et al. [15]	0, 3, 20, 44, 68 h PI	/	3, 10, 20, and 40 min and 1, 2, 4, 6, 20, 32, 44, 66 and 70 h PI	/	mono-exponential	OLINDA/EXM	61	0.9 $\pm$ 0.3	63 $\pm$ 18
	this study	/	4, 24, 168 h PI	0.5, 1, 4, 24, 168 h PI	/	bi-exponential	OLINDA/EXM	47	[0.61; 0.77; 0.98]	[51; 55; 60]
	Bergsma et al. [17]	24, 96, 168 h PI	/	0, 10, 30 min and 1, 1.5, 2, 6, 24 h PI	1, 6, 24, 48 h PI	PK model	OLINDA/EXM	23	0.067 $\pm$ 0.007	(NA)
	Del Prete et al. [19]	/	4, 24, 72 h PI	/	/	trapezoidal + mono-exponential	OLINDA/EXM	21	0.046 $\pm$ 0.033	(NA)
Red marrow	Forrer et al. [16]	/	3 between 0 and 24 h	5 between 0 and 168 h + bone marrow samples	first 24 h	(NA)	OLINDA/EXM	15	0.034 $\pm$ 0.030	(NA)
	Sandström et al. [11]	24, 96, 168 h PI	24, 96, 168 h PI	0.5, 1.0, 2.5, 4, 8, 24 h PI	first 24 h	trapezoidal + mono-exponential	self- and cross-dose	200	[0.012; 0.016; 0.022]	[39; 43; 51]
	Svensson et al. [20]	2, 24, 48, 168 h PI	24 h PI	/	/	bi-exponential	self- and cross-dose	46	0.027 $\pm$ 0.007	(NA)
	Wehrmann et al. [15]	0, 3, 20, 44, 68 h PI	/	3, 10, 20, and 40 min and 1, 2, 4, 6, 20, 32, 44, 66 and 70 h PI	/	tri-exponential	OLINDA/EXM	27	0.04 $\pm$ 0.02	23 $\pm$ 11
	this study	/	4, 24, 168 h PI	0.5, 1, 4, 24, 168 h PI	/	bi-exponential	OLINDA/EXM	47	[0.023; 0.028; 0.032]	[48; 52; 66]

Table 2

Minimum, first, second (median), and third quartile, and maximum (min[Q1;Q2;Q3]max) are presented for T_{max} (delay between injection and maximum point of TAC for kidneys, spleen and liver), T_{infl} (delay between injection and inflection point of TAC for red marrow and remainder of the body), a_{max} (activity in compartment normalized by injected activity at maximum point of TAC for kidneys, spleen and liver), a_{infl} (activity in compartment normalized by injected activity at inflection point of TAC for red marrow and remainder of the body), V (compartment's volume), T_{1/2 eff} (late effective half-life) and TIAC for kidneys, spleen, liver, red marrow and remainder of the body during the first ¹⁷⁷Lu-DOTATATE therapy cycle of 47 patients.

	T _{infl} /max [h]	a _{infl} /max [$\times 10^{-2}$]	V [mL]	T _{1/2 eff} [h]	TIAC [h]
Right kidney (N = 47)	0.1 [2.5; 6.7; 8.6] 14.4	0.8 [1.5; 1.9; 2.4] 5.9	105 [140; 174; 207] 352	26 [50; 55; 59] 94	0.7 [1.3; 1.6; 1.9] 6.3
Left kidney (N = 44)	0.1 [0.7; 6.8; 8.5] 14.9	0.7 [1.5; 1.8; 2.3] 5.7	101 [155; 173; 209] 299	22 [51; 55; 60] 99	0.7 [1.3; 1.6; 1.9] 7.2
Spleen (N = 42)	0.1 [0.3; 4.3; 8.2] 13.1	0.3 [1.5; 2.4; 3.7] 11.5	49 [139; 187; 317] 523	24 [68; 71; 77] 114	0.4 [1.5; 2.5; 3.7] 11.7
Liver (N = 47)	0.2 [0.6; 1.1; 6.1] 13.0	1.7 [6.3; 11.6; 30.8] 65.8	1014 [1396; 1865; 2649] 4711	29 [61; 79; 94] 127	1.6 [6.1; 15.2; 36.8] 99.7
Red marrow (N = 47)	0.0 [4.1; 5.5; 6.7] 9.5	0.2 [0.3; 0.4; 0.6] 1.4	NA	27 [48; 52; 66] 108	0.1 [0.2; 0.3; 0.4] 1.0
Remainder (N = 47)	0.1 [2.3; 3.3; 4.1] 8.5	4.8 [12.4; 17.1; 23.2] 98.3	46,812 [58764; 67728; 78186] 124,500	33 [70; 85; 98] 139	4.4 [9.1; 12.5; 14.3] 47.5

On the other hand, the evolution of activity over time for the remainder of the body and the blood was described by the sum of two decreasing exponentials resulting in a two-phase TAC. The first phase of the TAC (i.e. until 5–10 h PI) is thought to decrease rapidly with both the massive specific binding of ¹⁷⁷Lu-DOTATATE and the renal plasma clearance. The second phase decreases more slowly with combined residual specific binding, renal clearance and physical decay.

In the present work, the mean activity concentration was sampled with multiple small VOIs in a healthy homogeneous part of each source volume on SPECT images. This method was proposed and supported by Sandström et al. [35]. First, they showed that, compared to activity quantification on SPECT images, quantification based on planar images might artificially increase TIAC by 100% for the left kidney close to the spleen and by 50% for the right kidney close to the liver. Activity overestimation on planar images is further illustrated by the results presented in Table 1; dosimetry procedures based on planar images display higher kidney absorbed dose than SPECT-based or hybrid dosimetry methods. Second, they studied the impact of three common quantification methods on the computed absorbed dose to kidneys and spleen. The first method used one small VOI; the second used a large VOI delineated on anatomical CT; and the third used a large VOI segmented by thresholding on SPECT images. They concluded that the small VOI method had a smaller inter-observer variability and was the most time-efficient.

This conclusion is not completely in line with a recent Monte Carlo based study conducted by Vicente et al [36]. They recommended the use of a transaxial slice region of interest near the central plane of the organ to quantify activity on SPECT images in small organs such as kidneys. Their results indicated that activity quantification is very sensitive to a spherical VOI placement. In our study, the use of multiple VOIs allows the comparison of activity concentration in each VOI of a considered source volume and the evaluation of their correct positioning. Moreover, in Vicente et al. study, no post-filtering was applied to images, meaning that they are significantly impacted by noise. The 12 mm Gaussian post-filtering used for our SPECT images helped to reduce the impact of noise on quantification. It also helped for the visual placement of spheres in central homogenous organ area, reducing so the partial volume effect impact by sampling activity concentration in the centre of the considered source volume.

To estimate red marrow mass, we adapted the standard red marrow mass to the patient's height as previously proposed by Brindle et al. [24]. Hindorf et al. [37] summarized two other approaches: the standard red marrow mass was adapted either to the patient body mass or to the ratio between measured trabecular volume of lumbar vertebra and its standard volume. Regardless of the method used to estimate the red marrow mass, however, it is a significant error to overlook the remaining portion of active red marrow. Red marrow functionality may be widely impacted by previous therapies such as chemotherapy and, to a smaller proportion, radiotherapy [38].

In common with the majority of other groups (Table 1), the dosimetry methodology described here used OLINDA/EXM to compute

absorbed doses. Grimes et al. [39] have conducted an interesting comparison between ¹⁷⁷Lu computed absorbed dose with OLINDA/EXM and with the reference Monte Carlo simulation technique. When using OLINDA/EXM, organs were weighed for their true mass and the sphere model was used for tumour-meaning cross-dose was not taken into account for tumour dosimetry. Grimes et al. showed that computed absorbed doses were in very good agreement for both techniques (maximum error of 10%). Indeed, ¹⁷⁷Lu emits electrons with limited energy (maximum energy of 177, 385 and 498 keV with emission probability of 11.6, 9.1 and 79.3% respectively [40,41]) which travel along a short pathway in soft tissues; most of the absorbed dose is due to electron self-dose thus producing good results with the simplified OLINDA/EXM model.

Median kidney and red marrow absorbed doses obtained with the present dosimetry methodology were in accordance with other centres' results. These results vary widely between 0.55 and 1.15 Gy/GBq for kidneys and 0.016 and 0.067 Gy/GBq for red marrow (Table 1). Indeed, despite the fact that kidneys and red marrow are the main OAR in ¹⁷⁷Lu PRRT [17,33] and that their dosimetry was extensively studied during this last decade, there is still no consensus on how to conduct dosimetry properly. Although many parameters differ from one method to another, kidney dosimetry results clearly highlight the fact that due to organ overlapping, activity quantification on planar images is overestimated and the absorbed dose is artificially increased. This is further supported by the fact that an increased computed absorbed dose is not observed anymore when planar is combined with SPECT for quantification adjustment [11]. Results also indicate that using an early last time point (68 or 72 h PI) and/or a simplified fitting model might decrease the computed absorbed dose. Finally, higher variability for red marrow might be explained by the fact that a blood-based dosimetry relies on a sensitive well counter calibration and on reproducible sample activity quantification. On the other hand, when planar or SPECT images are used, the very low activity concentration in red marrow increases statistical noise in measurements.

Each step of the described dosimetry procedure was discussed, and possible solutions were compared in terms of additional patient burden, practicality and reproducibility. The resulting decisions were described in detail in this article in order to allow their implementation in a clinical context in other centres. Finally, the resulting dosimetry results for the two OAR (i.e. kidneys and red marrow) were compared to other dosimetry clinical data available in literature.

6. Conclusions

A dosimetry procedure was developed for OAR in ¹⁷⁷Lu-DOTATATE therapy based on SPECT/CT images in combination with blood samples. This pragmatic procedure was routinely implemented in a clinical context with limited patient burden. It was described and discussed in detail in this article in order to be repeatable in other centres. The observed variability of inter-centre dosimetry results highlights the need for sharing and standardizing detailed dosimetry procedures.

Standardized and comparable dosimetry results will contribute to a better understanding of the dose-effect relationship, potentially leading to individualized therapies and ultimately to therapeutic outcome improvement.

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of supporting data

All results are provided within the article and its additional file.

Authors' contributions

GM and BV conceived and designed the study; they developed, implemented and performed all patients' dosimetry. GM, BV, IK and PF analyzed and interpreted the data. GM drafted the manuscript. ZW, TG and IK critically reviewed the manuscript. PF, SV and NR helped write the paper. PF supervised the project. All authors read and approved the final manuscript.

Declaration of interest

None.

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Authors' information

Not applicable.

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