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Emerging need of dosimetry in radioligand therapy: a feasible method tested in a large cohort of patients affected by neuroendocrine neoplasms

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Abstract

Background: Radioligand therapy is an important treatment option for neuroendocrine neoplasms. Although the use of internal dosimetry is recommended, its application in clinical routine is not widespread. This study aims to propose and evaluate a feasible method for determining the absorbed doses to organs at risk and tumour lesions in a large cohort of neuroendocrine neoplasm patients.

Eighty patients who were treated as part of the FENET-2016 trial were enrolled in this study prospectively. The FENET-2016 protocol is based on two therapeutic schemes: a MONO therapy, consisting of five administrations (therapeutic cycles) of ^{177}Lu -DOTATOC and a DUO therapy, consisting of three cycles of ^{177}Lu -DOTATOC alternating with two cycles of ^{90}Y -DOTATOC. A simplified method based on three-time-point SPECT/CT was first validated on a small cohort of patients and was then applied to all the eighty patients enrolled in the study to assess dosimetric evaluation for the organs at risk (kidneys, bone marrow, and tumours).

Results: Sixty-nine patients underwent a complete dosimetric evaluation. Absorbed doses per administered activity and cumulative absorbed doses were reported for organs at risk and tumours, as well as biologically effective doses for organs at risk. The results of this study are consistent with published data from other groups. The cumulative absorbed dose to the kidneys exceeded the threshold reported in the literature in ten cases out of sixty-nine cases, while no cases of a cumulative absorbed dose exceeding 2 Gy to the bone marrow were reported. High variability in tumour absorbed dose per unit activity was observed.

Conclusions: The proposed simplified dosimetric approach is feasible and easy to implement in clinical practice. This study demonstrated that dosimetry is a useful clinical tool, as it enables clinicians to guide patients towards combined radionuclide treatment or multiple treatments, which could improve patient outcomes.

Keywords: Radioligand therapy, Neuroendocrine neoplasms, Dosimetry, ^{177}Lu , ^{90}Y

Trial Registration: EUDRACT 2016-005129-35, Registered 22 February 2018,
<https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-005129-35>

1. Introduction

Radioligand therapy (RLT) is an emerging strategy for cancer treatment that delivers radiation to selected cell types using a radioisotope and the cell-targeting compound. This approach is now an important option for the treatment of neuroendocrine neoplasms (NENs) [1-2], and it has recently been incorporated into cancer care guidelines for these tumour types. In NENs, RLT targets somatostatin receptors (SSTRs) on the surface of neuroendocrine tumour cells [3-4]. According to the results of the NETTER-1 trial [5], well-differentiated gastroenteropancreatic NENs are considered ideal candidates for RLT. However, any other tumour overexpressing SSTRs (e.g. bronchopulmonary NENs) could also be targeted for RLT [6]. Many clinical trials have confirmed that RLT is an effective and well-tolerated treatment, with only mild and transient hematologic and renal toxicities usually reported [6-9].

Dosimetry has played and continues to play an important role in RLT as an essential tool for calculating the radiation dose to balance the risks and benefits of the proposed administration. Among the proposed treatment protocols, the fixed activity administration regimen, such as the one proposed by Lutathera®, does not take into account the potential individual differences in biodistribution and tolerability of therapy. Conversely, treatment protocols tailored to dosimetry have the potential to individualize administrations to maximize the absorbed dose delivered to target lesions, thereby limiting unnecessary toxicity and ultimately improving treatment outcomes [3, 10-15]. Recently, dosimetry has become increasingly important, as evidenced by the European Union Regulation that recommends an individualized dose calculation for each radiation-based therapy, including nuclear medicine procedures [16-17].

The dosimetric studies on RLT with ^{177}Lu report that kidneys and bone marrow (BM) are the dose-limiting organs in RLT [18], even though ^{90}Y -based treatment is more frequently associated with renal toxicity [19-20]. Co-administration of amino acids has been shown to reduce the renal uptake to some extent, and thus the absorbed dose to the kidneys [21]. Similarly, BM toxicity results from the irradiation of hematopoietic tissues and could cause grade 3 or 4 haematologic toxicity in about 5-10% of patients [12, 22]. In addition, although rare, patients may develop late BM toxicity with occasional myelodysplastic syndromes or acute leukaemia as reported as in the literature. While kidney dosimetry has been extensively studied, BM dosimetry has been less thoroughly investigated due to technical limitations of the procedures [23-26]. However,

some studies have shown that the BM must be considered the dose-limiting organ in approximately 70% of patients treated with ^{177}Lu -DOTATATE [24].

As individualized dose calculation has been shown to be an important tool for patient treatment to improve the accuracy of absorbed dose calculation [27-28], various studies have been reported. These include different combinations of time-point measurements, mathematical or radiobiological models, organ- and voxel-scale dosimetry based on Monte Carlo simulations, individual phantoms for personalized sets of dose coefficients, new computer programs for biokinetic modeling and internal dose calculations [29-32]. Despite these advancements, there is still a lack of uniformity in the literature for RLT in NENs regarding dosimetry methodology, thresholds for absorbed doses in target lesions and organs-at-risk (OARs), optimal fractionation and activity to be administered. In addition, the challenges of a specialized staff training, patient discomfort during repeated imaging sessions, and the time required for image acquisition and dose calculation hinder the widespread implementation of dosimetry in clinical practice.

The present study aims to propose and evaluate the application of a reliable and clinically feasible dosimetry approach for a large cohort of NEN patients treated in our institute. In this study, dosimetry was performed during the first and last therapeutic cycle to monitor the absorbed doses by the organs at risk (kidneys and bone marrow) and by the tumour lesions representative of the disease.

2. Materials and Methods

2.1 Patients and RLT treatment

Eighty patients (50 males and 30 females; age 25-84, mean 64 years) treated in the FENET-2016 trial (EudraCT 2016-005129-35) from July 2018 to February 2020 were prospectively enrolled in this study. The FENET-2016 protocol includes patients affected by various forms of NEN with high somatostatin receptor expression of tumour lesions (targets, from here on) evaluated by ^{68}Ga -DOTATOC PET/CT study [33]. Detailed information on patients' selection criteria and on therapeutic approach are described in a previously published paper [33].

According to the FENET-2016 protocol, the treatment is based on a first therapeutic level consisting of five RLT cycles, one every 8-10 weeks, followed by a possible second therapeutic level of three RLT cycles. Two therapeutic schemes can be used at the first level. The first scheme, called MONO RLT, consists of five administrations of ^{177}Lu -DOTATOC. The second scheme, called DUO RLT, consists of three administrations of ^{177}Lu -DOTATOC alternating with two administrations of ^{90}Y -DOTATOC. **Figure 1** summarizes the therapeutic schemes used for RLT at first therapeutic level.

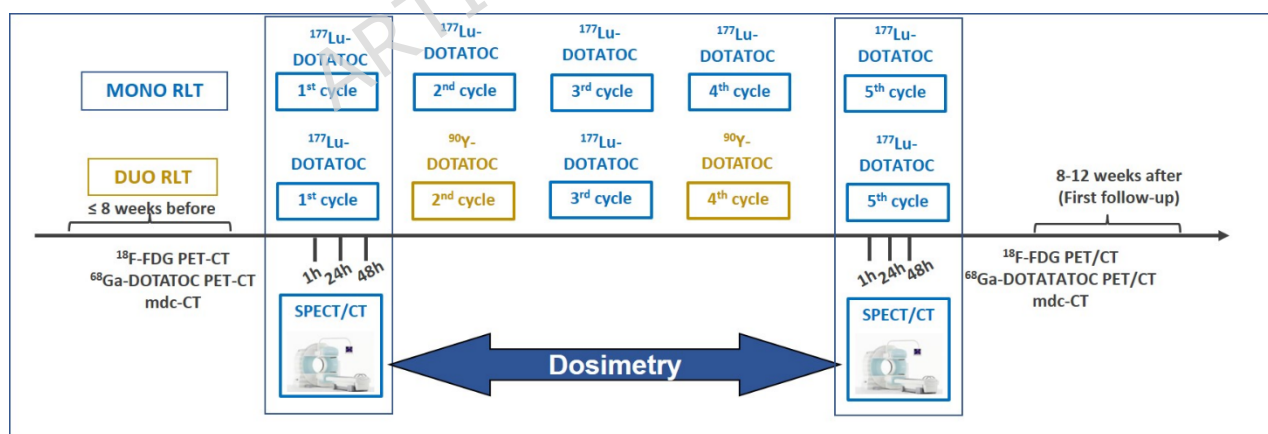


Figure 1 Therapeutic scheme used for RLT in FENET-2016 protocol.

A dosimetric assessment was performed for each patient at the first and last cycles (1st and 5th cycle). The activity administered at the first treatment cycle was individualized based on each patient's characteristics, including renal function, hematologic profile, lesion size and location, performance status, and comorbidities. Subsequent cycles were instead adjusted according to patient-specific dosimetry results. Patients presenting risk factors—such as low blood counts, impaired renal function or performance status, very large lesions with potential risk of edema due to their location, or significant comorbidities—received lower administered activities compared with other patients.

The administered activities at the first cycle were chosen based on the patient's status and the experience reported by the clinicians, while the subsequent administrations were guided by the results of the dosimetry.

The preparation of ^{90}Y -DOTATOC or ^{177}Lu -DOTATOC continues to be manually [4] according to national guidelines [NBP-NM, **Norme di Buona Preparazione dei Radiofarmaci per Medicina Nucleare**, G.U. n. 168, 07/21/2005] and in accordance with the Investigational Medicinal Product Dossier (IMPD) approved by the Italian authority (Agenzia Italiana del Farmaco, AIFA/SC/P/20572, 22 February 2018). The radiopharmaceutical was administered by peripheral intravenous injection. To ensure adequate hydration and protect the kidneys during the radiopharmaceutical excretion, all patients received arginine before, during and after the treatment injection. Patients were hospitalized in isolation rooms during and for the 48 hours after radiopharmaceutical administration. All procedures and staff training were performed in accordance with radioprotection regulations.

2.2 Dosimetric workflow

2.2.1 Imaging protocol

A preliminary study was conducted to define a simplified and feasible imaging protocol to apply to the entire cohort of eighty patients. This preliminary study, conducted on a cohort of seven patients out of the eighty enrolled, aimed to evaluate the impact of reducing imaging acquisitions on the dosimetric accuracy. For these seven patients, dosimetry based on SPECT/CT acquisitions with five time points (5TP) at 1, 24, 48, 72 and 96 h was compared with a simplified dosimetry using three time points (3TP) at 1, 24, 48 h. The absorbed doses to the kidneys, BM, and target lesions obtained with 5TP were compared with those obtained with 3TP to evaluate the accuracy of the latter method despite the reduced number of image acquisitions. Based on the results of this preliminary study, the patient imaging protocol for the large cohort of eighty patients included three abdominal SPECT/CT acquisitions at 1, 24 and 48 h (3TP) after the radiopharmaceutical administration. This protocol was applied to each patient undergoing RLT during both the first and the last cycles.

Image acquisition was performed using a Siemens Symbia Intevo T series gamma camera, equipped with medium-energy general purpose (MELP) collimators. Energy windows were centered at 113 keV and 208 keV (15% width), with a 128×128 matrix, 64 projections, and 30 seconds per view.

The gamma camera was properly calibrated to determine the Calibration Factor (CF) and Recovery Coefficient (RC). A cylindrical Jaszczak phantom filled with a ^{177}Lu solution (0.41 ± 0.02 MBq/ml) was used to derive the CF. The RC values were evaluated using the NEMA PET phantom equipped with five spheres (1.35, 2.5, 5.0, 11.0 and 26.0 ml) filled with a ^{177}Lu solution (46 ± 3 MBq). Further details regarding the calibration procedures and results are described in a previously published paper [34]. The acquired SPECT projection images were reconstructed using the Flash 3D OSEM iterative reconstruction software at the Symbia.net workflow station. The aforementioned iterative algorithm applies scatter, attenuation, and collimator detector response corrections to the projection data as suggested by Ljungberg et al. [35].

2.2.2 Contouring

Contouring of OARs and targets was performed on the three sequential SPECT/CT scans using the MIM[®] Maestro workstation. A personalized and semi-automated workflow facilitated the contouring of the kidneys and the L2-L4 lumbar vertebrae segment, utilizing co-registered CT images for guidance (**Figure 2**).

OARs were contoured at the first cycle on the 48-hour SPECT scan using thresholding-based segmentation. These contours were then automatically propagated to the 24-hour and 1-hour SPECT studies of the first cycle. The same contours were also propagated to the last cycle. Targets were selected and delineated at the first cycle by the nuclear medicine physician on the 48-hour SPECT scan, using thresholding-based segmentation with a fixed threshold of 50%. These contours were automatically propagated to the 24-hour and 1-hour SPECT studies (**Figure 2**). The contouring of the targets was re-evaluated at the last cycle. As a result, the volume of the targets remains constant across the different time points within each cycle but varied between the first and last cycles.

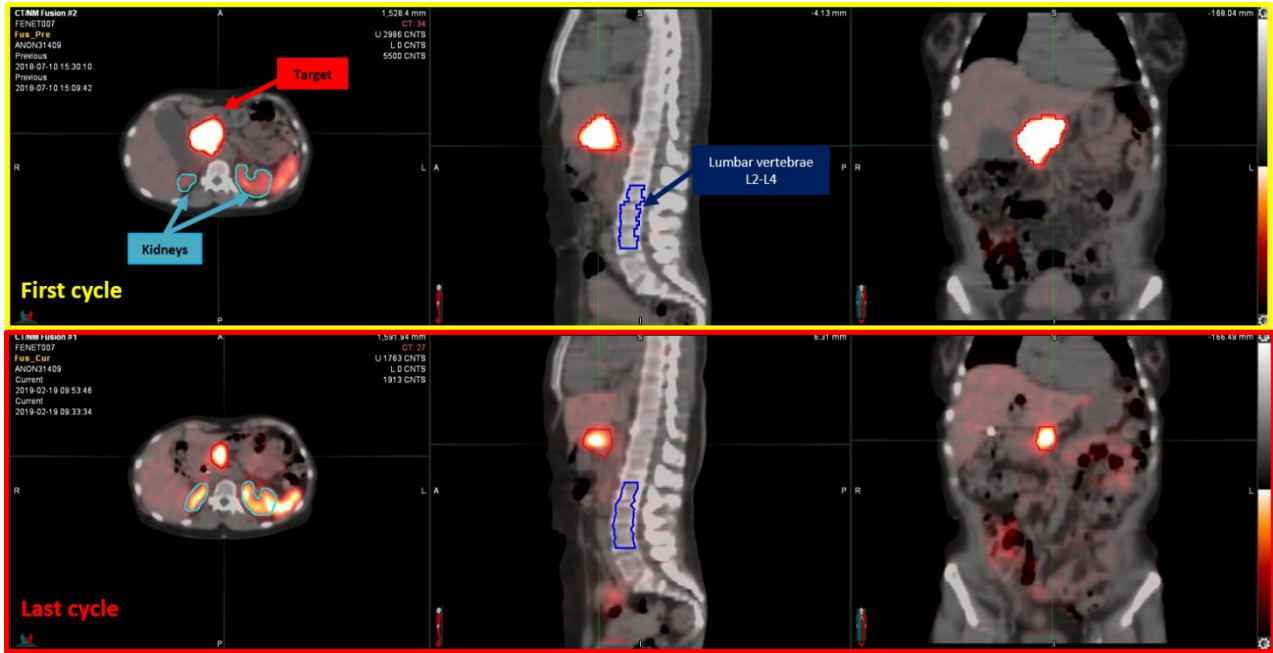


Figure 2 Example of segmentation of the OARs and targets at first and last cycles via MIM® Maestro workstation using SPECT/CT data and segmentation propagation for kidneys and BM.

The software allows for the generation of a complete report of total counts and counts per ml as a function of acquisition time for each selected volume of interest (VOI). The contouring of the targets and OARs enabled the evaluation of the deposited activity at the three time points (1, 24 and 48 h) after the injection [36].

2.2.3 Dose calculation

Dose estimates for each patient were determined according to the MIRD scheme [36-38] by calculating the absorbed doses to the OARs, specifically the kidneys and BM, as well as the targets. Using the activity-time curve (TAC), the effective half-life and the absorbed doses for the organs and target tissues were obtained using the software OLINDA/EXM v2.2. Both the standard organ masses included in the software and the personalized organ masses derived from CT scans [39] were considered. The mean absorbed target doses were estimated using the unit density sphere module of the software.

For BM dosimetry, the patient's BM was delineated on the trabecular portion of the L2-L4 lumbar vertebrae, and the corresponding mass was calculated by scaling the reference man value based on the measured volumes [29]:

$$m_{L2-L4}^{patient} = m_{L2-L4}^{ref.man} \times \frac{V_{L2-L4}^{patient}}{V_{L2-L4}^{ref.man}}$$

The TAC was calculated by fitting the data obtained from contouring at 1, 24 and 48 hours. This was done to determine the absorbed dose to the BM ("self-dose" contribution), based on the assumption that the BM mass in L2-L4 represents 6.7% of the total BM mass. The S-value for the BM, as tabulated in MIRD Pamphlet no. 11 [24-25, 40], was used in the calculation:

$$D_{RM}^{patient} = \frac{\bar{A}_{L2-L4}^{patient}}{0.067} \times S_{ref.man}^{(RM \leftarrow RM)} \times \frac{V_{L2-L4}^{ref.man}}{V_{L2-L4}^{patient}}$$

Since SPECT/CT studies were performed only during the 1st and 5th cycles, the dosimetric evaluation at the 2nd, 3rd and 4th cycles of MONO RLT (those involving only with ^{177}Lu -DOTATOC) was achieved by scaling the absorbed dose per administered activity calculated for the 1st cycle to the actual administered activity.

For the intermediate cycles of DUO RLT (those involving ^{90}Y -DOTATOC administration at 2nd and 4th cycles), the SPECT image counts were also rescaled to account for the difference in half-life between the two isotopes. Since the pharmaceutical vector (DOTATOC) is the same, the biodistribution of ^{90}Y was assumed to be identical to that of ^{177}Lu . The activity values obtained from image quantification with ^{177}Lu at 1 h, 24 h and 48 h were scaled according to the different administered activity and the different half-life of the isotope, ensuring that the biological uptake and washout remained unchanged.

OLINDA/EXM was then used to calculate the absorbed dose. For the 3rd cycle in DUO RLT (those with the ^{177}Lu -DOTATOC), the dosimetric evaluation was performed by scaling the absorbed dose per administered activity calculated for the 1st cycle to the actual administered activity.

The Biological Effective Doses (BED) were calculated for the OARs using the linear-quadratic model, according to the formula:

$$\text{BED} = \sum_i D_i + \frac{\beta}{\alpha} \frac{\lambda}{\lambda + \mu} \sum_i D_i^2$$

where D_i is the absorbed dose in the i -th cycle, m is the exponential repair rate constant, λ is the effective clearance rate, and α and β are the tissue-specific radiation damage coefficients with a proportional to dose and b proportional to dose squared [41]. The parameter λ is calculated as the sum of the physical decay and the biological clearance rate constants, while μ , α and β are those reported in [41] for kidneys and BM. The cumulative absorbed doses (cAD) and BEDs for a given treatment are calculated as the sum of the absorbed doses and BEDs obtained in each cycle, respectively.

2.3 Statistical analysis

Regarding the study on the effect of imaging acquisition reduction on dosimetric accuracy, a correlation analysis was performed between the absorbed doses estimated by the 3TP method (Y variable) to those estimated by the more refined 5TP method (X variable) for both OARs and targets. For this purpose, an unbiased linear regression of the form $Y = aX$ was derived, and the estimator $\hat{a}$ for the parameter a was determined using the maximum likelihood algorithm,

$$\hat{a} = \frac{\sum_{j=1}^n X_j Y_j}{\sum_{j=1}^n X_j^2}$$

where (X_j, Y_j) represents the sample for the bivariate variable (X, Y) . In our case, the sample size was $n=7$ for all the analysed cases. The goodness of fit was assessed by calculating the Pearson correlation coefficient, r , for the linear fit assuming a standard error level of $\alpha=0.01$ of first type, and the corresponding p -values were computed. Additionally, a paired t-test was performed between the 3TP and 5TP methods results to test the null hypothesis H_0 which states that the average difference between the results of a series of paired observations is zero.

Regarding the data from the entire cohort of eighty patients, the dosimetric results were compared between MONO and DUO RLT, as well as between 1st and 5th cycles. Statistical analysis was performed using two-tailed t-test with a significance level of 0.95. This analysis was based on the statistical toolbox of Matlab (The Mathworks, Natwick, MA).

The dispersion of the absorbed doses and relative quantities for OARs and targets is presented using box plots. In these plots, the central tick indicates the median of the data; the boxes extend from the 25th to the 75th percentiles; and the whiskers extend to the most extreme data points, excluding outliers (beyond 2.7σ), which are displayed as individual points.

2.4 Uncertainties evaluation

As with the vast majority of software for clinical applications, OLINDA/EXM v2.2 does not provide uncertainty estimates for the absorbed dose. An estimation of these uncertainties was provided (see the Results section) by considering the main factors affecting the absorbed dose calculation according to the MIRD scheme [37-39]: the counts registered by SPECT/CT, the gamma camera's CF and the S-values.

Regarding the counts registered by SPECT/CT, it can be assumed that the uncertainty in counts registration follows Poisson statistics, so the statistical uncertainty when measuring N counts is

$\sqrt{N}$. For the gamma camera's CF, data are reported by Di Domenico et al. [34]. These two contributions were summed in quadrature to have an estimation of the uncertainty associated with each activity value for each VOI. Each activity value was corrected for the partial volume effect (PVE), according to the RC curve reported by Di Domenico et al. [34]. TACs were fitted with the same function used by OLINDA/EXM v2.2 but using the software Igor Pro v4.01 that provides error estimation for each fit parameter.

Regarding the uncertainty associated to S-values, in principle, one can expect that, since they are all obtained via Monte Carlo simulation, the associated uncertainty is at least of the order of $\sqrt{N}$, where N is the number of events simulated in ICRP phantoms used for the simulation. Since the number of simulated events is typically large, it can be assumed that the uncertainty associated to the S-values is not comparable to the uncertainty associated to the time-integrated activity.

3. Results

3.1 Patient population

Among the 80 patients who underwent RLT with ^{177}Lu - and ^{90}Y -DOTATOC, not all received a complete dosimetric evaluation. Eleven patients were excluded from the dosimetric study due to early treatment discontinuation or technical issues, such as incomplete SPECT/CT studies, which prevented accurate dosimetric assessment. Details of the 69 patients who underwent a complete dosimetric evaluation are summarized in **Table 1**.

Table 1 Details on the 69 patients that underwent a complete dosimetric evaluation.

PATIENTS		MONO RLT (39)	DUO RLT (30)	Total MONO and DUO RLT (69)
GENDER, number (%)	Male	25 (64.1)	18 (60.0)	43 (62.3)
	Female	14 (35.9)	12 (40.0)	26 (37.7)
AGE, median [IQR]		60 [48÷69]	68 [58.5÷73]	64.5 [52÷71]
ORIGIN, number (%)	P	18 (46.1)	15 (50.0)	33 (47.8)
	M	9 (23.1)	4 (13.3)	13 (18.8)
	B	5 (12.8)	3 (10.0)	8 (11.6)
	U	3 (7.7)	4 (13.3)	7 (10.1)
	SA	2 (5.1)	1 (3.3)	3 (4.3)
	O	2 (5.1)	3 (10.0)	5 (7.4)

P: Pancreatic NETs; M: midgut NETs; B: bronchial NETs; U: Unknown primary origin NETs (CUP-NETs); SA: Sympathetic-Adrenergic axis NETs; O: others; nd: not defined.

Among these 69 patients, 39 were treated with MONO and 30 with DUO RLT with a mean injected activity of 4.9 GBq (range 3.5-6.5 GBq) and 2.9 GBq (range 2.2-4.7 GBq) for each cycle of ^{177}Lu and ^{90}Y , respectively. All 69 patients underwent dosimetric evaluation in the kidneys, 44/69 in the BM, and 69/69 in the targets at the 1st cycle, while 65/69 patients underwent evaluation in the targets at the 5th cycle. Detailed information on the number of dosimetric calculations performed with MONO and DUO RLT at the 1st and 5th cycles is shown in **Table 2**.

Table 2 Details on number of dosimetric studies performed with MONO and DUO RLT.

	Number of dosimetric studies			
	1 st cycle		5 th cycle	
	MONO RLT	DUO RLT	MONO RLT	DUO RLT
Kidneys	39	30	39	30
Bone marrow	28	16	28	16
Targets	39	30	36	29

For the BM, in some cases, the presence of metastasis in L2-L4 did not allow the dosimetric evaluation. For the targets, both primitive lesions and metastases were considered, with at least one lesion per patient, whenever possible. Lesions with irregular or inhomogeneous distributions

were excluded from the study, as these characteristics make the application of the sphere model unsuitable; moreover, at 5th cycles, no captation in some tumour lesions made the dosimetric evaluation inapplicable.

3.2 Imaging protocol

This section reports the results of the preliminary study conducted to investigate the feasibility of a simplified imaging protocol. The absorbed doses calculated using 5TP and 3TP methods for the cohort of seven patients are summarized in **Table 3**.

Table 3 Absorbed doses calculated with 5TP and 3TP for kidneys, BM and targets for the cohort of seven patients.

Patient's number	Absorbed dose (Gy)					
	Kidneys		Bone Marrow		Targets	
	3TP	5TP	3TP	5TP	3TP	5TP
FENET 1	2.76 ± 0.28	2.84 ± 0.21	0.21 ± 0.02	0.19 ± 0.01	12.6 ± 5.9	14.4 ± 3.2
FENET 2	2.86 ± 0.31	3.40 ± 0.27	0.25 ± 0.02	0.23 ± 0.02	10.1 ± 0.9	9.8 ± 3.3
FENET 3	4.62 ± 0.95	4.80 ± 0.41	0.12 ± 0.01	0.11 ± 0.01	9.4 ± 4.8	11.2 ± 2.7
FENET 4	2.35 ± 0.38	1.78 ± 0.14	0.11 ± 0.01	0.11 ± 0.01	16.4 ± 4.8	18.7 ± 2.6
FENET 5	1.89 ± 0.21	2.06 ± 0.17	0.15 ± 0.02	0.16 ± 0.01	7.6 ± 3.5	8.2 ± 1.6
FENET 6	2.05 ± 0.23	2.13 ± 0.17	0.14 ± 0.02	0.13 ± 0.01	10.6 ± 1.1	8.7 ± 2.9
FENET 7	1.43 ± 0.14	1.66 ± 0.13	0.19 ± 0.02	0.17 ± 0.01	11.8 ± 4.2	12.5 ± 1.8

The effect of reducing imaging acquisition on dosimetric accuracy was evaluated. The correlation between the absorbed doses estimated by the 5TP and 3TP methods was significant for kidneys, BM, and tumour lesions (**Table 4**).

Table 4 Results of correlation between the absorbed doses estimated with 5TP and 3TP for kidneys, BM and targets.

	Pearson Correlation coefficient	p-value	
Kidneys	0.95	<0.01	correlated variables
Bone Marrow	0.98	<0.01	correlated variables
Targets	0.94	<0.01	correlated variables
	Paired t-test two tailed result	p-value	H ₀
Kidneys	0.4454	> 0.05	True
Bone Marrow	0.0609	> 0.05	True
Targets	1.26	> 0.05	True

3.3 Dosimetric studies

The results of the dosimetric studies for all patients who underwent dosimetry are reported below for the kidneys, BM, and targets, in terms of effective half-lives, absorbed doses (AD) per administered activity, AD and BED.

3.3.1 Kidneys dosimetry

Kinetics for the kidneys showed similar behaviour among different patients. The TACs for the kidneys were fitted using either a mono- or a bi-exponential function.

In most of the patients, an initial rapid washout followed by a slower decline was observed; in these cases, the renal uptake curves were fitted by a mono-exponential function, resulting in a

longer effective half-life. In a few cases, a maximum uptake was observed between 1 and 24 hours, followed by a rapid washout; in these cases, a bi-exponential fit function was used.

For the kidneys, the effective half-life was 43.1 ± 15.4 h (mean $\pm$ SD) for the 1st cycle and 44.8 ± 15.5 h for the 5th cycle. The variation in effective half-life between the 1st and 5th cycles was not statistically significant for the kidneys (p-value = 0.44).

The ADs per administered activity obtained for the kidneys are reported in **Figure 3(a)** for the 1st and 5th cycles for MONO RLT and in **Figure 3(b)** for the 1st, 2nd and 5th cycles for DUO RLT. The median AD to the kidneys per cycle was 2.7 Gy (range 0.8-6.3 Gy) for the 1st cycle (¹⁷⁷Lu, MONO and DUO RLT), 7.6 Gy (range 1.2-18.9 Gy) for the 2nd cycle (⁹⁰Y, only for the DUO RLT protocol) and 2.7 Gy (range 0.7-7.2 Gy) for the 5th cycle (¹⁷⁷Lu, MONO and DUO RLT).

The mean AD per single administration calculated for ⁹⁰Y was approximately five times higher than that for ¹⁷⁷Lu, with a mean factor of 4.9 for the kidneys (median 5.3, range 2.2-6.2).

The mean increase in the cADs to the kidneys was 76% when using DUO compared to MONO RLT. The variations in cAD between MONO and DUO RLT were statistically significant for the kidneys (p-value < 0.001). In 10 cases, all involving patients undergoing the DUO RLT protocol, the cAD to the kidneys exceeded the threshold reported in the literature of 28 Gy (23 Gy for patients with risk factors).

Figure 3(c) shows the comparison between the BED for MONO and DUO treatments for the kidneys, while **Figure 3(d)** shows the behaviour of the BED as a function of cAD. For the kidneys, the median extra contribution to the BED from the cAD increased with increasing absorbed dose and was 1.30 Gy (range 0.1-12.2 Gy). Considering a maximum tolerated absorbed dose of 23 Gy to the kidneys, the dose-limiting organ was the kidney in 15% of the patients. With a maximum tolerated BED of 28 Gy to the kidney, the kidney was the dose-limiting organ in 9% of the patients.

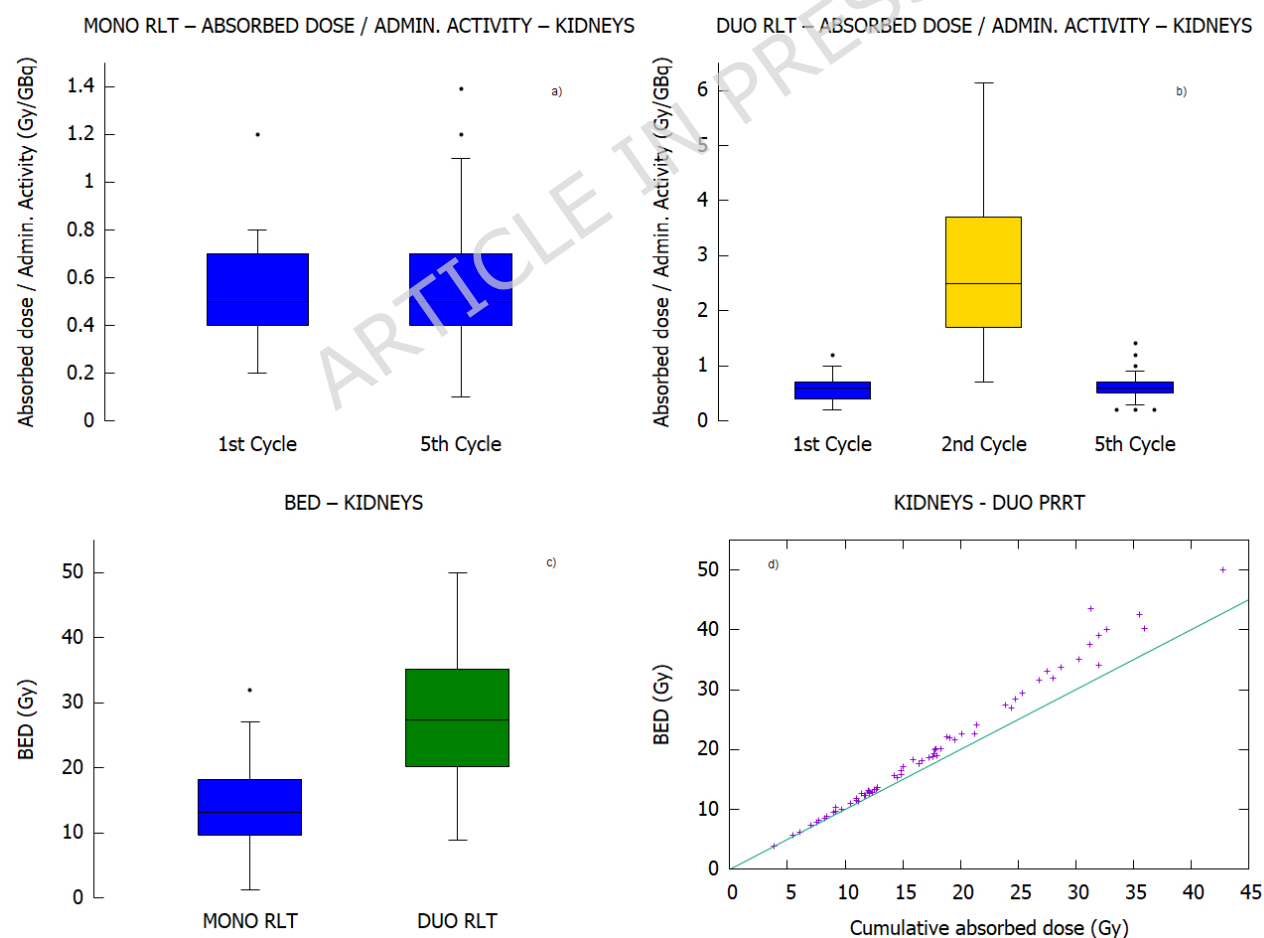


Figure 3 Absorbed doses per administered activities for kidneys for MONO (a) and DUO (b) RLT. BED for MONO and DUO RLT (c) and correlation between BED and AD (d) for kidneys.

3.3.2 Bone marrow dosimetry

TACs for BM were fitted based on the hypothesis of biodistribution from the compartment model reported in [42]. The fit of the fraction of injected activity in L2-L4 (FIA_{L2-L4}) was performed using a 3-parameter exponential decay model:

$$FIA_{L2-L4} = e^{-\lambda_{ph}t}(A + B \cdot e^{-\lambda_1 t})$$

where λ_{ph} is the inverse of ^{177}Lu mean lifetime and is fixed.

The BM TACs showed a similar trend for most patients, resulting in an effective half-life of 5.99 ± 2.25 h (mean $\pm$ SD) for the 1st cycle and 6.68 ± 2.14 h for the 5th cycle. The variations in effective half-life between the 1st and 5th cycles were statistically significant for the BM (p-value = 0.042).

The ADs per administered activity obtained for BM are reported in **Figure 4(a)** for the 1st and 5th cycles of MONO RLT and in **Figure 4(b)** for the 1st, 2nd, and 5th cycles of DUO RLT.

The median AD to BM per cycle was 0.13 Gy (range 0.04-0.42 Gy) for the 1st cycle (^{177}Lu , MONO and DUO RLT), 0.24 Gy (range 0.02-0.49 Gy) for the 2nd cycle (^{90}Y , only for the DUO RLT protocol) and 0.13 Gy (range 0.04-0.34 Gy) for the 5th cycle (^{177}Lu , MONO and DUO RLT).

The mean AD per single administration calculated for ^{90}Y were approximately five times higher than those for ^{177}Lu , with a mean factor of 4.4 for BM (median 4.5, range 2.0-8.0). No cases exceeding the cAD of 2 Gy to bone marrow were reported. The mean increase in the cADs to BM was 30% when using DUO compared to MONO RLT. The variations in cAD between MONO and DUO RLT were not statistically significant for BM (p-value = 0.12).

Figure 4(c) shows the comparison between the BED for MONO and DUO treatments for BM, while **Figure 4(d)** shows the correlation between BED and cAD. The cAD and BED values for BM were approximately equal.

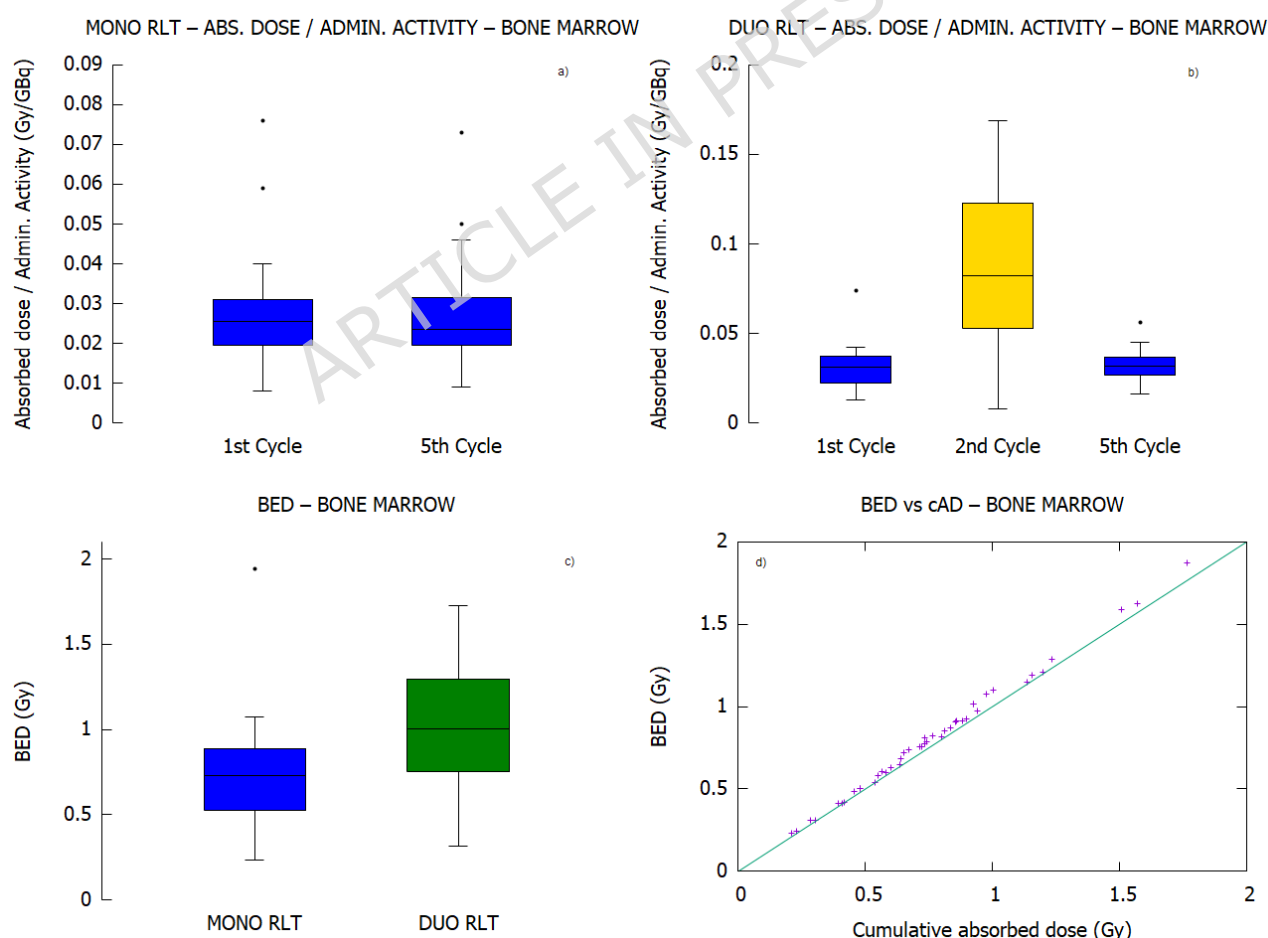


Figure 4 Absorbed doses per administered activities for BM for MONO (a) and DUO (b) RLT. BED for MONO and DUO RLT (c) and correlation between BED and AD (d) for BM.

3.3.3 Targets dosimetry

Most frequently, the TACs for target lesions showed a rapid increase between 1 and 24 hours, followed by a slower washout; these curves were fitted with a bi-exponential function.

For the targets, the effective half-life was 81.1 ± 25.7 h (mean $\pm$ SD) for the 1st cycle and 81.7 ± 28.7 h for the 5th cycle. Differences in uptake were observed among targets, as this depends on factor such as localization, target type, and tumour volumes. The variations in effective half-life per administered activity between the 1st and 5th cycles were not statistically significant for targets (p-value = 0.77).

Table 5 summarizes the target volumes evaluated at the 1st cycle and the reduction in uptake volumes between the 1st and 5th cycles for MONO and DUO RLT.

Table 5 Targets' volumes evaluated at 1st cycle and variation of captation volumes between 1st and 5th cycles (both expressed as mean [range]) for MONO and DUO RLT.

Target volume evaluated at 1 st cycle (ml)		Variation of captation volume between 1 st and 5 th cycles* (%)	
MONO RLT	DUO RLT	MONO RLT	DUO RLT
39 [3÷437]	59 [8÷490]	-19 [-100÷76]	-45 [-97÷50]

*The negative values correspond to a reduction of the captation volume.

Figure 5(a) and **(b)** show the differences in ADs per administered activities between MONO and DUO RLT.

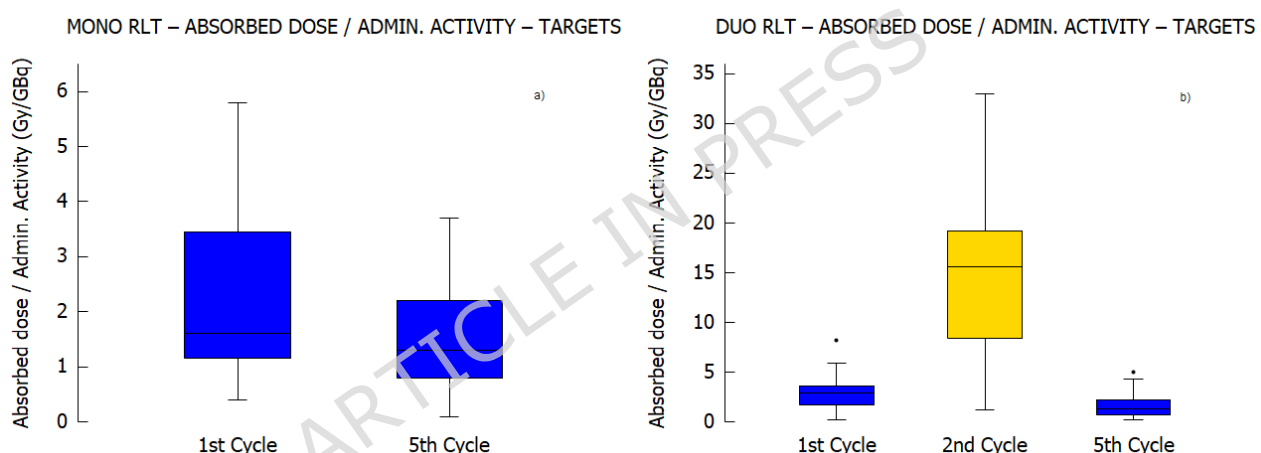


Figure 5 Absorbed doses per administered activities for targets for MONO a) and DUO b) RLT. Results are shown per cycle: 1st and 5th for MONO, 1st, 2nd and 5th for DUO RLT.

The ADs to targets per cycle were: 11.9 ± 7.6 Gy (mean $\pm$ SD) for the 1st cycle (¹⁷⁷Lu, MONO and DUO RLT), 39.9 ± 21.8 Gy (mean $\pm$ SD) for the 2nd cycle (⁹⁰Y, only for the DUO RLT protocol) and 7.6 ± 5.6 Gy (mean $\pm$ SD) for the 5th cycle (¹⁷⁷Lu, MONO and DUO RLT).

3.4 Overall dosimetric results

For the purpose of reporting the overall dosimetric results, the absorbed doses per administered activity (AD per admin. activity) and absorbed doses (AD) at the 1st, 2nd, and 5th cycles, as well as the BED for OARs and the cumulative absorbed dose (cAD) for targets, are resumed in **Table 6**.

Table 6 Absorbed doses per administered activity and absorbed doses at 1st, 2nd and 5th cycles, BED for OARs and cumulative absorbed dose for targets. Data are expressed as mean/median [range] or mean $\pm$ SD.

AD per admin. activity (Gy/GBq) mean [range]	Kidneys	Bone Marrow	Targets
1 st cycle	0.55 [0.20÷1.20]	0.027 [0.008÷0.076]	2.5 [0.20÷8.20]

2nd cycle	2.8 [0.7÷6.1]	0.083 [0.008÷0.169]	14.1 [1.20÷33.0]
5th cycle	0.58 [0.10÷1.40]	0.028 [0.009÷0.073]	1.5 [0.10÷5.00]
AD (Gy) median [range] or mean ± SD	Kidneys	Bone Marrow	Targets
1st cycle	2.7 [0.8÷6.3]	0.13 [0.04÷0.42]	13.8 [0.6 - 83.2]
2nd cycle	7.6 [1.2÷18.9]	0.24 [0.02÷0.49]	13.4 [0.8 - 86.0]
5th cycle	2.7 [0.7÷7.2]	0.13 [0.04÷0.34]	7.9 [0.2 - 32.6]
	Kidneys	Bone Marrow	Targets^{a,b}
BED (Gy) median [range]	13.2 [1.3÷31.9]	0.81 [0.23÷1.94]	-
cAD (Gy) mean ± SD	-	-	79.0 ± 57.4

^aTargets' BED are not reported, as coefficients for BED calculation are not provided by literature for targets.

^bFor targets the cumulative absorbed dose is reported.

4. Discussion

In the present study, we proposed a simplified dosimetric protocol applied to a large cohort of NEN patients who underwent RLT. We analyzed dosimetric data of sixty-nine patients after ¹⁷⁷Lu-DOTATOC and ⁹⁰Y-DOTATOC RLT individualized treatment protocols during both first and last cycles of administrations. The proposed dosimetric protocol proved to be reliable, feasible and compatible with the high number of treated patients. Balancing costs and benefits, our study proposed a dosimetry based three time points acquisitions at first and last cycle, evaluating absorbed doses to OAR (kidneys and bone marrow) and tumour lesions.

The cumulative absorbed dose to the kidneys exceeded the threshold reported in the literature (28 Gy, or 23 Gy for patients with risk factors) in ten out of sixty-nine cases; all of these cases involved patients undergoing the DUO RLT protocol. No cases exceeding the cumulative absorbed dose of 2 Gy to bone marrow were reported. A decrease in ADs to tumour lesions was observed with a drastic reduction in uptake volumes between the first and last cycles for both MONO and DUO RLT.

Our study also demonstrated that first-cycle dosimetry could be useful for predicting the absorbed dose to the kidneys and BM, while for lesions, a dosimetric re-evaluation is recommended at least during the last cycle.

Currently, ¹⁷⁷Lu-DOTATATE/DOTATOC and ⁹⁰Y-DOTATOC are among the most clinically used radio-peptides for the treatments of NENs. ⁹⁰Y is particularly suitable for radionuclide therapy, but not for imaging. Reported experiences with ⁹⁰Y-DOTATOC yielded favorable results particularly in larger tumors [13], while the major concern is related to the high renal dose delivered [43]. The physical properties of ¹⁷⁷Lu offer some advantages with respect to ⁹⁰Y: it is suitable for both imaging and therapy [18] and it may reasonably exert a more favorable effect on small tumors (<2 cm) and micro-metastases. All studies agree in reporting absorbed dose to OARs lower for ¹⁷⁷Lu as compared with ⁹⁰Y.

Despite its utility has been already established in clinics, RLT still determines a growing interest in clinical context and feeds the planning of further studies. New radiopharmaceuticals are under development and new perspectives pursue to identify the most suitable radiopharmaceutical in terms of efficacy and safety or combinations of radiopharmaceuticals (¹⁷⁷Lu- and ⁹⁰Y-radiopeptides) which are promising for the treatment of different-sized lesions.

Although there is a general agreement in the literature on the importance of individualized therapy using dosimetry as a tool for individual risk assessment for sensitive organs, the use of the personalized approach, such as the one employed in this study, remain a topic of debate [44]. On one hand, the individualized approach can be safely used to calculate the amount of administered radioactivity, which should be 'as high as reasonably possible' to achieve an

optimal treatment outcome. Dosimetry is highly dependent on patient pharmacokinetics, as there is a high inter-patient variability. Thus, this approach requires personalized analysis and accurate quantification of input data, including the timing of measurements for correct estimation of the time-integrated activity and the accuracy of the absorbed dose calculations. Furthermore, proponents suggest that dosimetry-based optimization should be added to the registration, in addition to fixed treatment schemes, to allow for clinical dosimetry [45].

On the other hand, other studies recognize the role of dosimetry in radiopharmaceutical development and safety, but they claim its clinical use as not evidence based. Moreover, they emphasize caution when transitioning from the well-established and safe empirical dosage schemes towards the complex, time-consuming, and non-standardized dosimetry approaches [46]. This opinion is also based on the general beliefs that a minimum number of measurements are required also including the late time points, such as up to 4 to 7 days after treatment. Such requirements tend to increase both the clinical burden and patient inconvenience when a personalized approach is applied, thereby limiting the widespread clinical adoption of dosimetry [31]. From a clinical perspective, fixed-activity regimens are known to result in conservative safety thresholds for OARs in most patients, even though current cure rates are marginal, suggesting that most patients are being undertreated with the empiric RLT regimen. Moreover, standardizing treatment is challenging due to the wide range of disease statuses, histological tumour types, and treatment histories [31].

The recently published EANM position paper for nuclear medicine therapy [47] includes therapies based ^{90}Y -DOTATOC and other ^{177}Lu - or ^{90}Y -labelled SSTR ligands for the treatment of neuroendocrine diseases among the non-standardized therapies and classifies dosimetry as advisable at level L2 (activity-based prescription and patient-specific dosimetry). Level 2 compliance is reached by recording and reporting of the absorbed dose to organs at risk and optionally the absorbed dose to treatment regions for the individual patient. Dosimetry in RLT typically requires multiple post-therapy SPECT/CT scans [48], but data collection is often discontinued on the second or third day after therapy for logistical reasons. The protocol used in this study is based on dosimetry performed using three time-points (i.e. SPECT/CT scans at 1, 24 and 48h after treatment). Our experience demonstrated that this simplified approach represents a feasible tool for faster therapy management and a viable method to improve the patient's comfort.

However, the limited number of SPECT/CT acquisitions over time in the proposed protocol could affect the accuracy of the time-activity curve determination, particularly for sites with longer washout periods, where a late time-point acquisition (e.g. 72 hours) could be relevant. Another limitation of our study lies in the fragmented workflow used for the dosimetric purposes, which could increase the likelihood of errors and is time-consuming, requiring significant resource allocation. Moreover, to address the lack of deeper validation of our method, further investigation could be directed to the inter-comparison of the used methodology with systems used in other centres of with approved software.

Despite the discussed limitations and the significant variation reported in the literature regarding average absorbed doses for OARs and tumours due to differences in methodology and patient characteristics, the average absorbed doses calculated using our simplified, yet personalized methodology fall well within the range of published data from other groups, as reported in **Table 7**. Based on our experience, the significant inter-individual variations and the need to effectively treat patients with different disease statuses, histological tumour types and treatment histories suggest that an individualized dosimetric approach should be recommended.

Table 7 Comparison of the main studies and their dosimetric results obtained in different centres (expressed as mean $\pm$ SD or median [range]) for ^{177}Lu -DOTATATE treatments.

Author	No. of patients	Method	OAR		Targets	
			Organ	Absorbed dose (Gy/GBq)	Site (total number)	Absorbed dose (Gy/GBq)
Kwekkeboom et al. [49]	5	Planar imaging	Kidneys Liver Spleen	0.62 [0.45÷17.74] 0.18 [0.05÷0.34] 0.64 [0.29÷2.91]	Tumour	[0.6÷56]]
Cremonesi et al. [43]	10	Planar imaging	Kidneys Liver	0.88 $\pm$ 0.19 0.21 $\pm$ 0.08	Tumour	[3.9÷37] .9]

			Spleen	2.15 ± 0.39		
Wehrmann et al. [18]	27	Planar imaging	Whole body Kidneys Spleen	0.05 ± 0.02 0.9 ± 0.3 1.2 ± 0.5	Liver (104) Lymph node (49) Bone (19) Pancreas (11) Soft tissue (10)	12.4 ± 15.1 8.0 ± 8.4 5.4 ± 4.4 3.0 ± 2.9 5.8 ± 4.0
Forrer et al. [24]	15	SPECT/CT imaging	Red marrow	0.034 ± 0.030	NA	NA
Cemonesi et al. [50]	10	Planar imaging	Kidney Bone marrow	0.62 [0.45÷17.74] 0.04 [0.02÷0.06]	Tumour	[0.6÷56]
Garkavij et al. [21]	16	Planar imaging	Kidneys	0.97 ± 0.24	Tumour	6.7 [0.1÷20]
Larsson et al. [7]	33	Planar imaging	Kidneys	0.80 ± 0.30	NA	NA
Gupta et al. [13]	61	Planar imaging	Liver Kidneys Spleen Pituitary gland	0.27 ± 0.05 0.57 ± 0.09 1.17 ± 0.14 0.058 ± 0.011	Tumour	3.41 ± 0.68
Kairemo et al. [51]	7	SPECT/CT imaging	Kidney Bone marrow	1.15 [0.54÷2.16] <0.07	Tumour	[2÷11]
Sandström et al. [10]	200	Planar imaging	Kidney Bone marrow	0.61 [0.47÷0.73] 0.016 [0.012÷0.022]	NA	NA
Ilan et al. [53]	24	SPECT/CT imaging	NA	NA	Pancreas (24)	6.7 [1.3÷23.0]
Svenson et al. [19]	51	Planar imaging	Kidneys	0.63 ± 0.2	NA	NA
Svenson et al. [54]	46	Planar imaging	Red marrow	0.027 ± 0.007	NA	NA
Bergsma et al. [12]	23	Planar imaging	Red marrow	0.067 ± 0.007	NA	NA
Bergsma et al. [55]	407	Planar imaging	Kidneys	0.67 ± 0.20	NA	NA
Del Prete et al. [14]	36	SPECT/CT imaging	Kidney Bone marrow	0.55 ± 0.20 0.046 ± 0.033	Tumour (maximum)	4.2 ± 2.9
Sandström et al. [52]	500	Planar imaging SPECT/CT imaging	Right kidney Left kidney	4.4 [1.7÷9.8] 4.2 [1.1÷9.8]	NA	NA
Sundlöv et al. [28]	51	Planar imaging	Kidneys	0.61 [0.3÷1.98]	NA	NA
Marin et al. [30]	47	SPECT/CT imaging	Kidneys Spleen Red marrow	0.78 ± 0.35 1.07 ± 0.58 0.028 ± 0.010	NA	NA
Santoro et al. [56]	12	SPECT/CT imaging	Kidneys Liver Spleen Red marrow	0.43 ± 0.13 0.54 ± 0.58 0.61 ± 0.13 0.04 ± 0.02	NA	NA
Del Prete et al. [15]	52	SPECT/CT imaging	Kidney Bone marrow	0.54 [0.24÷4.25] 0.035 [0.004÷0.216]	Tumour (maximum)	4.4 [0.1÷32.0]
Pirozzi Palmese et al. [57]	30	SPECT/CT imaging	Kidneys Spleen	I Cycle	Tumor lesions	6.2 ± 3.4

			Liver Red marrow	0.5 ± 0.2 [0.2÷0.8] 0.6 ± 0.4 [0.1÷1.9] 0.9 ± 0.9 [0.1÷3.8] 0.018 ± 0.008 [0.009÷0.045]		[0.3÷14 .6]
Present study	80	SPECT/CT imaging	Kidney Bone marrow	0.6 [0.1÷1.4] 0.027 [0.008÷0.076]	Tumour sites	2.5 [0.1÷8. 2]

NA: Not available.

5. Conclusions

This work showed that, from a clinical point of view, RLT is safe for almost all patients. This study demonstrated that dosimetry represents a useful tool for clinicians, enabling them to guide patients toward combined radionuclide treatment or multiple treatments, thus potentially improving patient outcomes. In the present study, the simplified dosimetric approach was shown to be feasible and easy to implement in clinical routine. The application of dosimetry represents a highly advantageous strategy, not only for individual risk-assessment of OARs in toxicity monitoring but also for target dose evaluation. An advanced use of dosimetry could, in the near future, encompass toxicity monitoring, target dose evaluation, and dose-response correlation, potentially revealing eventual correlations between tumour shrinkage and absorbed dose.

Abbreviations

AD Absorbed Dose
 BED Biological Effective Dose
 BM Bone Marrow
 cAD cumulative Absorbed Dose
 CT Computed Tomography
 MIRD Medical Internal Radiation Dosimetry
 NEN Neuroendocrine Neoplasm
 OAR Organ At Risk
 PET Positron Emission Tomography
 RLT Radioligand Therapy
 SD Standard Deviation
 SPECT Single-Photon Emission Computed Tomography
 SSTR Somatostatin Receptor
 TAC Time Activity Curve
 3TP 3 Time Points
 5TP 5 Time Points

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Author contribution: All the authors contributed to the study. Mariaconcetta Longo and Eugenia Tonini equally performed study conception and design; Mirco Bartolomei performed patients' selection and management; Luca Urso and Corrado Cittanti performed patients' data acquisition; data analysis was performed by Giovanni Di Domenico, Lorenzo Longo and Christian Macis; data preparation was performed by Mariaconcetta Longo, Eugenia Tonini, Giovanni Di Domenico and Lorenzo Longo; Licia Uccelli performed radiopharmaceuticals management; Ilaria Panzini performed technical support for clinical protocol validation, Alessandro Turra provided physical knowledge of the dosimetry methods. The first draft of the manuscript was written by Mariaconcetta Longo, Eugenia Tonini, Giovanni Di Domenico and all the authors commented on earlier versions of the manuscript. All the authors read and approved the final version of the manuscript.

Data availability

The datasets used and/or analyzed during the current study are not publicly available due to data protection policies but are available from the corresponding author on reasonable request.

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Declarations

Ethics approval

"This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Provincia di Ferrara (Date 13 October 2016/CE 160990)."

Clinical Trial registration:

- EU Clinical Trials Register, EUDRACT Id: 2016-005129-35, 22 February 2018.
<https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-005129-35>
- ClinicalTrials.gov, Clinical Trials ID: NCT04790708, 02 March 2021.
<https://clinicaltrials.gov/study/NCT04790708>

Consent to participate

"Informed consent was obtained from all individual participants included in the study."

Consent to publish

"The authors affirm that human research participants provided informed consent for publication of the images in Figure 2."

Competing Interests

"The authors have no relevant financial or non-financial interests to disclose."

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