STM JOURNALS

Research & Reviews: A Journal of
Medical Science and Technology

ISSN: 2319-3417 (Online)
ISSN: 2349-1272 (Print)
Volume 12, Issue 2, 2023
DOI (Journal): 10.37591/RRJoMST

https://medicaljournals.stmjournals.in/index.php/RRJoMST/index

Research RRJoMST

Activity Quantification of Lu-177 SPECT/CT Imaging for Calibration Factor Analysis in Clinical Radionuclide Dosimetry

Madhulika Mehrotra[1,*], Sanjana Ballal[2], Prashant Mishra[3], C.S. Bal[4]

Abstract

Purpose: *To evaluate the calibration factor (CF) at three-time points with the same protocol & acquisition parameters for the images of Lu-177 activity, scanned by two different SPECT/CTs (GE & MEDISO) using a cylindrical Jaszczak phantom with cold inserts, filled with uniform activity in water and to analyze the changes in the calibration factor data with time. The purpose of the study is to quantitatively analyze the first step (calibration acquisition) in clinical dosimetry workflow.* ***Methods:*** *The study was performed two times as SET-I and SET-II, with a gap of six months with the same phantom and SPECT/CTs for three-time points (Day 0, Day 4 & Day 7). A known activity of Lu-177 was filled in the Jaszczak phantom with uniform activity in the water solution. The scans were performed by the two dual- headed SPECT/CTs (GE & MEDISO) with high energy general purpose (HEGP) collimator. To calculate the calibration factor, the counts are evaluated from reconstructed images for the same volume of interest (VOI) to convert into the activity.* ***Results:*** *In the SET-I study, the CFs obtained from GE SPECT/CT showed that the CF remains approximately constant for two-time points (Day 0 & Day 7) and was less on Day 4. For MEDISO SPECT/CT, the CF remains approximately constant for two-time points (Day 4 & Day 7), but on Day 0, the CF was less. In the SET-II study, the CF obtained from GE SPECT/CT and MEDISO SPECT/CT, at three-time points shows that the CF remains approximately constant for the uniformly distributed Lu-177 activity in the phantom.* ***Conclusion:*** *Our study supports that uniform activity distributed over the entire phantom volume and reconstructed images obtained from the SPECT/CT with attenuation & scatter corrections are essential steps for accurately evaluating calibration factors in clinical dosimetry workflow.*

***Author for Correspondence**
Madhulika Mehrotra
E-mail: madhulikamehrotra@gmail.com

[1]Women Scientist Fellow, Department of Nuclear Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[2]Medical Physicist, Department of Nuclear Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[3]Student, Department of Nuclear Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[4]Professor and Head, Department of Nuclear Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Received Date: July 20, 2023
Accepted Date: July 25, 2023
Published Date: August 18, 2023

Citation: Madhulika Mehrotra, Sanjana Ballal, Prashant Mishra, C.S. Bal. Activity Quantification of Lu-177 SPECT/CT Imaging for Calibration Factor Analysis in Clinical Radionuclide Dosimetry. Research & Reviews: A Journal of Medical Science and Technology. 2023; 12(2): 9–22p.

Keywords: calibration factor, Lu-177, SPECT/CT, clinical radionuclide dosimetry, Jaszczak phantom

INTRODUCTION

Targeted radionuclide therapy (TRT) [1], also referred to as peptide receptor radionuclide therapy (PRRT) [2] or molecular radiotherapy (MRT) [3] for neuroendocrine tumors (NETs) is a technique in which a radiopharmaceutical consisting of a radionuclide attached to a biologically active molecule represented as the receptor is administered to the patient. A therapeutic radionuclide in targeted radionuclide therapy using a beta-emitter has a short range in tissue to absorb the dose within the targeted region while sparing the surrounding healthy tissues. Peptides exhibit rapid pharmacokinetics (distribution, absorption, metabolism and excretion of the drug) and a good ability to penetrate efficiently into the tumor region.

The Lutetium (^{177}Lu) [4] radionuclide is used in TRT [5] due to its favorable decay characteristics and reliable labeling with biomolecules, especially for NET treatment. ^{177}Lu-DOTATATE has a carrier peptide (Octreotate) [6] that performs strong binding with the somatostatin receptors [7] that are present on the surface of NET cells; that id why it is the most commonly used radiopharmaceutical in PRRT for the treatment of NET patients. ^{177}Lu-DOTATATE, also known as Lutathera® [8], has been approved by the European Medical Agency (EMA) in 2017 and by the Food and Drug Administration (FDA) in 2018 for the treatment of NET patients. The personalized treatment approach allows a significant shift from a one-size-fits-all approach [9] (where the fixed amount of activity is administered to all patients) to a patient-specific treatment approach [10] (where the specifically assessed optimal amount of activity is administered to an individual patient). Bardiès and Gear [11] have demonstrated in their work the importance of patient-specific treatment in PRRT [12] to improve the treatment outcomes and reduce the toxicity in healthy tissues.

Patient-specific treatment planning requires the clinical dosimetry chain, which consists of several steps, starting with image acquisition to the absorbed dose calculation [13]. The accuracy of the dosimetric chain relies on the accuracy of each step involved in obtaining the absorbed doses, as defined by the Medical Internal Radiation Dose Committee (MIRD).

Personalized dosimetry in radionuclide therapy [14, 15] is based on: (1) quantitative imaging (including the acquisition settings, image reconstruction and corrections for absolute quantification), (2) pharmacokinetic assessment (including image registration, segmentation and time-integration of activities), and (3) the computation of absorbed dose in clinical dosimetry workflow. Figure 1 represents the clinical radionuclide internal dosimetry workflow (Cited from, 3rd and 11th ECMP and AIFM symposium, 16-19 June 2021, virtual edition, on "Dosimetry in Nuclear Medicine" by Manuel Bardies), that performs six steps: (1) Calibration acquisitions, (2) Patient Image acquisitions, (3) Reconstruction and Corrections, (4) Registration and Segmentation, (5) Time activity curve fittings and (6) Absorbed dose calculations (Mora-Ramirez et al. 2020) [16, 11].

The purpose of the study was to quantitatively analyze the first step, which is the calibration acquisition of the hybrid SPECT/CT (single photon emission computed tomography with computed tomography) [17] imaging to visualize the absolute activity distribution of ^{177}Lu activity in the volume of interest (VOI) across the patient's body. For accurate activity quantification in the patient study, it is necessary to convert the counts in the reconstructed images into the activity with the correction for the image degrading factors (such as attenuation, scatter, spatial resolution, partial volume effect, artifact, dead-time, etc.)

Quantitative imaging with the hybrid SPECT/CT [18, 19] has become an essential component in quantifying radiotracer distribution in PRRT. The direct measurement of activity distribution within the

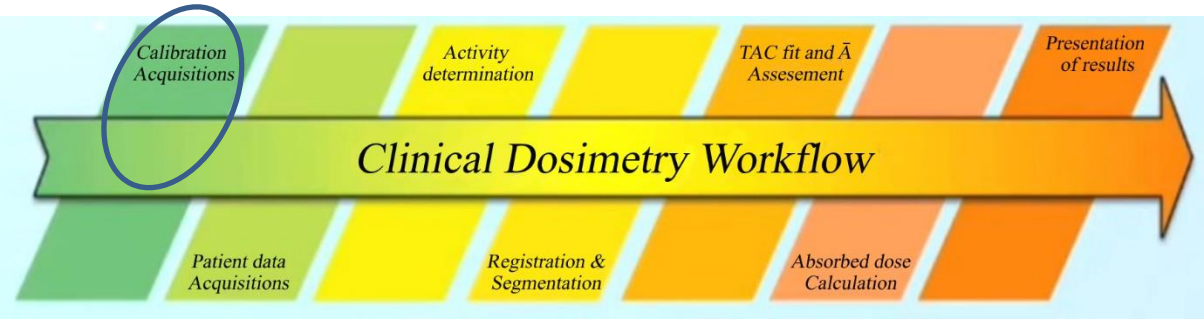


Figure 1. The clinical radionuclide internal dosimetry workflow (Mora-Ramirez et al. 2020) [16, 11]. (*Source: Bardies and Gear (2021) Scientific Developments in Imaging and Dosimetry for Molecular Radiotherapy. Clinical Oncology 33(2) 117-124*)

source region (phantom) requires calibration to convert the detected counts into the activity of a specific radionuclide, which is defined as the calibration factor (CF) [20–22] expressed in counts per second per MBq (cps/MBq). For calibrating the SPECT/CT, in order to calculate the CF, the phantom should be prepared carefully with uniform distribution of the known amount of activity of the Lu-177 radionuclide [23]. The calibration factor depends on the different types of gamma cameras, radionuclides and reconstruction settings/software [4, 14].

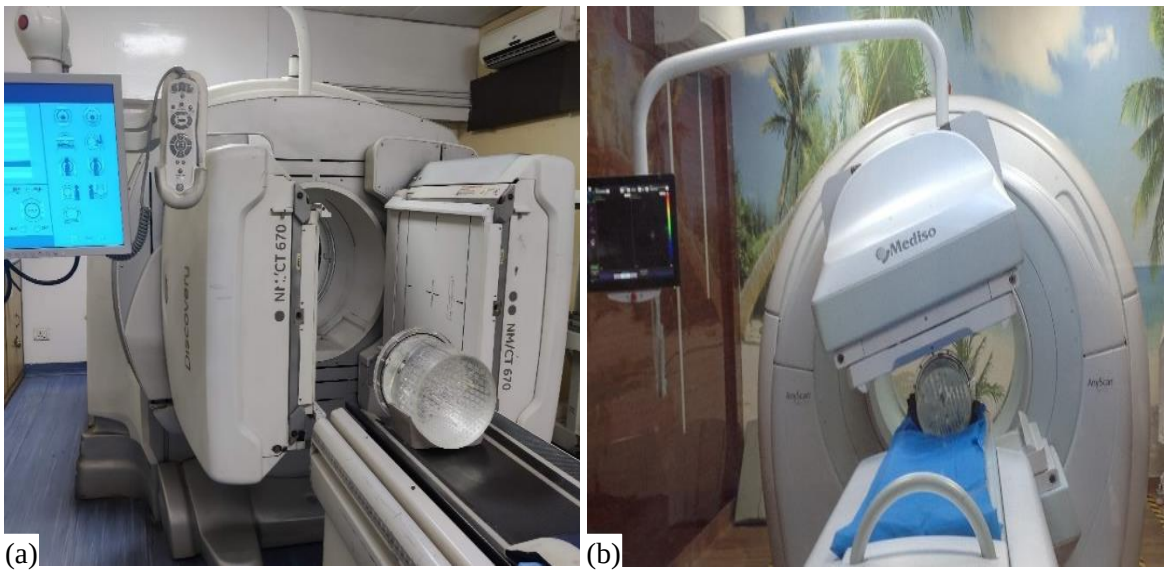
The study aims to calculate and analyze the CF, at three time points with the same acquisition parameters and protocol, for the image scanned by two different SPECT/CTs, using a large cylindrical Jaszczak phantom with cold inserts and filled with uniform activity in water. To analyze the change in the calibration factor data with time, the study is repeated after a gap of 6 months for the same phantom and SPECT/CTs referred to as SET-I and SET-II studies.

MATERIALS AND METHODS

The objective of this study was to measure the CF using images from SPECT/CT acquisitions of cylindrical Jaszczak phantom filled with Lu-177 activity at three time points similar to the patient study. To analyze the changes in the calibration factor data with time, the study was repeated after a gap of 6 months for the same phantom and SPECT/CTs represented as SET-I, for the first study and SET-II, for the second study. A standard protocol was followed for the analyses of the CF based on the recommendations of MIRD Pamphlets No. 23, 26 and ICRU Report 96 [4, 14, 24].

Data Acquisition

First of all, a known activity of ^{177}Lu (In SET-I study; 370 MBq and SET-II study; 399.23 MBq) with a half-life of 6.65 days, was filled in a large cylindrical phantom (Jaszczak phantom), with cold inserts and uniformly distributed activity in water with a volume of 6.09 L in SET-I study and 6.06 L in SET-II study. The scans were performed by two SPECT/CTs for three time points (Day 0, Day 4, and Day 7) using a dual-headed GE Healthcare, Discovery NM 630 SPECT/CT and MEDISO Nucline ANYSCAN 3.05.025.0000 SPECT/CT, with high-energy general purpose (HEGP) collimator. All the scans were performed at the Nuclear Medicine Department, All India Institute of Medical Sciences (AIIMS), New Delhi, India. The experimental configurations of the Jaszczak phantom positioned in the center of the SPECT/CT field of view of GE and MEDISO are shown in Figure 2. The phantom and SPECT/CT acquisition parameters details are described in Tables 1 and 2.



(a) (b)

Figure 2. The experimental configuration of the Jaszczak phantom in GE and MEDISO SPECT/CT (a) Dual-headed GE SPECT/CT and (b) dual-headed MEDISO SPECT/CT.

Table 1. Phantom parameter details.

S.N.	Phantom parameter	SET-I	SET-II
1	Cylindrical phantom	Jaszczak Phantom	
2	Phantom position	Center	
3	^{177}Lu half-life ($T_{1/2}$)	6.65 days (159.6 hours)	
4	Activity (A_0)	370 MBq / 10 mCi	399.23 MBq / 10.79 mCi
5	Weight of empty phantom (X)	3.090 kg	3.05 kg
6	Weight of phantom with activity in water solution (Y)	9.100 kg	9.110 kg
7	The volume of phantom with activity in water solution (Y-X)	6.09 kg or 6090 cm^3	6.06 kg or 6060 cm^3

Table 2. SPECT/CT acquisition parameter details.

S.N.	Acquisition parameters	SPECT/CT (GE) / (MEDISO)
1	SPECT/CT- GE	Dual-headed GE Healthcare, Discovery NM 630 SPECT/CT
2	SPECT/CT- MEDISO	Dual-headed MEDISO Nucline ANYSCAN 3.05.025.0000 SPECT/CT
3	Collimator (crystal thickness)	HEGP (high-energy general purpose) (3/8 inches)
4	Energy window width	20% triple energy window (TEW)
5	Photopeak energy (keV)	208, 113
6	Matrix size	128 × 128
7	Detector movement	Step and shoot
8	SPECT movement	Body contour
9	Projection per detector	60
10	Time of acquisition (SPECT)	12 min (GE) and 20 min (MEDISO)
11	Low-dose CT	120 keV/100 mA
12	Image reconstruction workstation	INTERVIEW-FUSION
13	Reconstruction algorithm	OSEM (ordered subset expectation maximization) (4 subsets / 48 iterations).

Image Reconstruction and Corrections

The ^{177}Lu decays by β^- emissions with the maximum kinetic energy of 498.3 keV, used in the therapy of NET patients for PRRT. ^{177}Lu also emits a range of gamma radiations with two prominent energy peaks at 113 keV (6.4%) and 208 keV (11%), which is used for diagnostic purposes. To perform the scatter correction [25, 26], the high-energy general purpose (HEGP) collimators were set for the Lu-177 therapy protocol by the GE and MEDISO engineers, with the triple energy window (TEW) [27] for both 113 keV and 208 keV photopeak windows, along with 20% energy window width (medium-energy collimator (ME) was not available in our department). The image reconstruction was performed using INTERVIEW-FUSION workstations, with 4 subsets and 48 iterations applying the ordered subset expectation maximization (OSEM) algorithm [28]. The CT-based attenuation correction was included in the reconstruction using the low-dose CT acquisition data [4, 14, 24]. The dead-time effect at three time points was not considered, as the amount of activity in the phantom was kept very low. The decay correction was applied during the acquisition of images of the phantom by the GE and MEDISO SPECT/CT system installed by the manufacturer. The reconstructed images by the SPECT and CT acquisition for the SET-I study and SET-II study are shown in Figures 3 and 4.

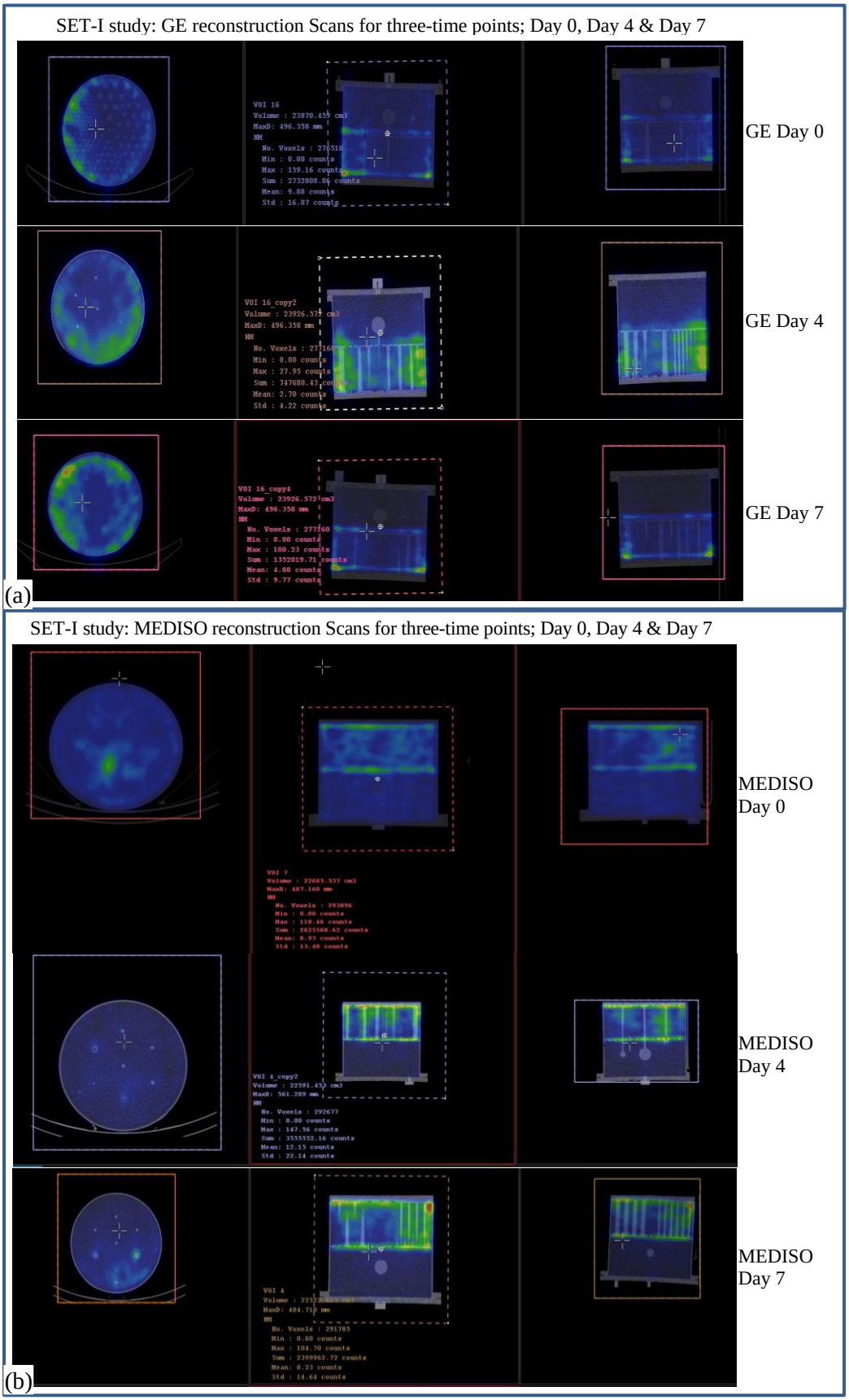


Figure 3. The reconstructed images for evaluation of the counts, by the SPECT & CT scan acquisition data for SET-I study, of GE & MEDISO SPECT/CT.

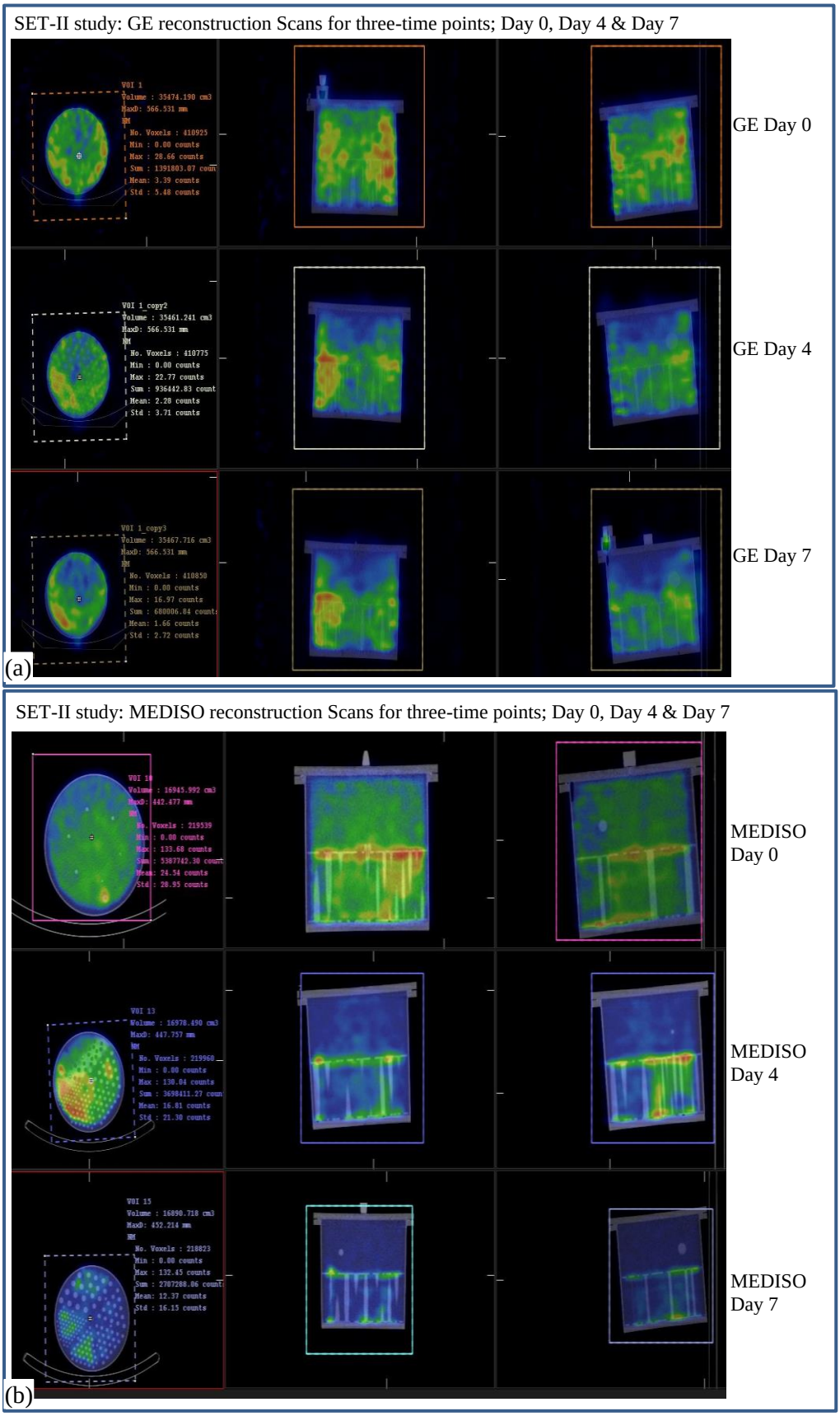


Figure 4. The reconstructed images for evaluation of the counts, by the SPECT & CT scanned acquisition data for the SET-II study, of GE & MEDISO SPECT/CT.

Image Quantification Analysis

The activity quantification of Lu-177 SPECT/CT imaging for evaluation of CF in clinical radionuclide dosimetry workflow was derived using the equation [21]:

$$CF = C / A * T$$

where CF is the calibration factor represented in the units of counts per second per MBq (cps/MBq); C is the counts in the reconstructed images of the phantom within the volume of interest (VOI), expressed in counts (c); T is the time of acquisition of images measured in seconds (s) and A is the activity ($A = A_0 e^{-\lambda t}$; decay factor of Lu-177, $\lambda = 0.693 / T_{1/2}\ h^{-1} = 0.0043421\ h^{-1}$; t is the time at the scan on Day 0, Day, 4 and Day 7) in the phantom at the time of acquisition measured in MBq. We have calculated the counts (C) using the following steps: (1) SPECT/CT scans of the Jaszczak phantom were taken for the three time points by the two SPECT/CTs (GE and MEDISO); (2) the scanned images were reconstructed using Interview and Fusion workstations; (3) the VOIs were drawn around the reconstructed images of the Jaszczak phantom for the three time points, on all the three planes; and (4) volume (in cm^3) of each VOI was kept approximately the same for each set of SPECT/CTs. The counts for each VOI, for each three time points, were noted for the same volume, to calculate the calibration factor as shown in Figures 5 and 6, and Table 3.

RESULTS

The datasets acquired from the SET-I study and SET-II study for the calculation of CF are shown in Tables 3 and 4, including the comparison of quantitative analyses of CF results for GE and MEDISO SPECT/CT at the three time points.

Table 3. Quantitative analyses of calibration factor for ^{177}Lu activity in SET-I study.

	Quantity	Day 0	Day 4	Day 7
GE SPECT/CT	Counts (C)	27,32,808.06	7,47,680.43	13,52,019.71
	Time at scan (t) (h)	5.17	100.3	172.267
	Activity (A) (MBq)	361.786	239.364	175.124
	Time (T) (s)	720	720	720
	Calibration factor (CF) cps/MBq	**10.491**	**4.338**	**10.722**
MEDISO SPECT/CT	Counts(C)	26,25,560.62	35,55,552.16	23,99,962.72
	Time at scan (t) (h)	2.833	101.1166	189.600
	Activity (A) (MBq)	365.476	238.517	162.428
	Time (T) (s)	1200	1200	1200
	Calibration factor (CF) cps/MBq	**5.986**	**12.422**	**12.312**

Table 4. Quantitative analyses of calibration factor for ^{177}Lu activity in SET-II study.

	Quantity	Day 0	Day 4	Day 7
GE SPECT/CT	Counts(C)	13,91,803.07	9,36,442.83	6,80,006.84
	Time at scan (t) (h)	19.083	113.633	187.367
	Activity (A) (MBq)	367.483	243.747	176.968
	Time (T) (s)	720	720	720
	Calibration factor (CF) cps/MBq	**5.260**	**5.335**	**5.336**

MEDISO SPECT/CT	Counts(C)	53,87,742.30	36,98,411.27	27,07,288.06
	Time at scan (t) (h)	19.883	114.333	187.850
	Activity (A) (MBq)	366.208	243.007	176.597
	Time (T) (s)	1200	1200	1200
	Calibration factor (CF) cps/MBq	**12.260**	**12.682**	**12.775**

The graphical analysis of the calibration factor results represented in Tables 3 and 4 is shown in Figures 5 and 6, respectively.

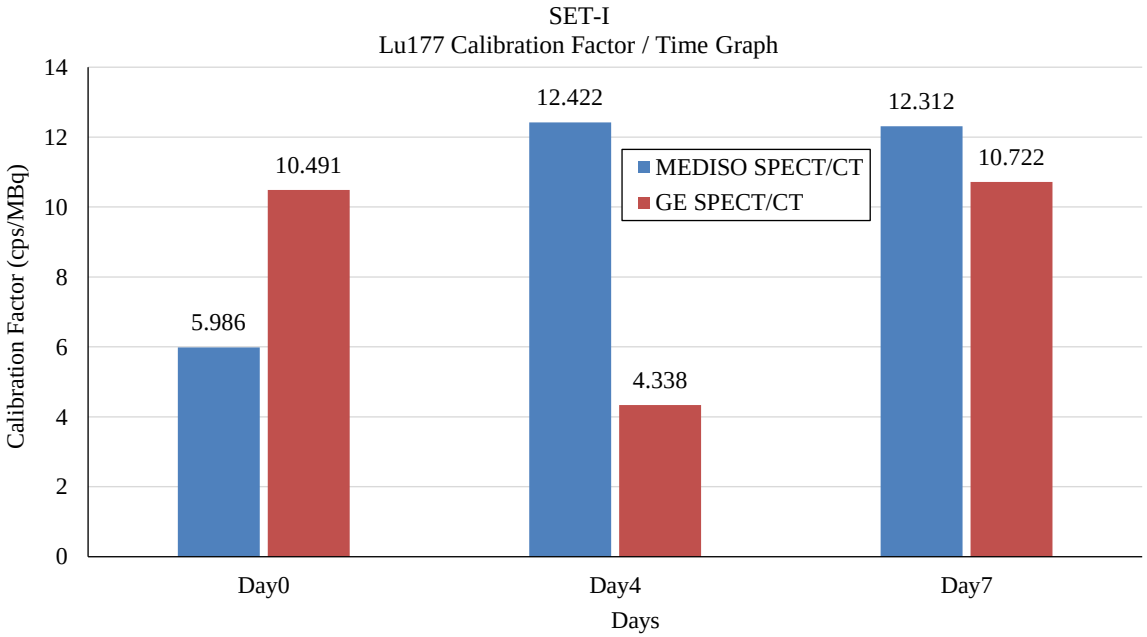


Figure 5. Analyses of calibration factor values for each SPECT/CT in the SET-I study.

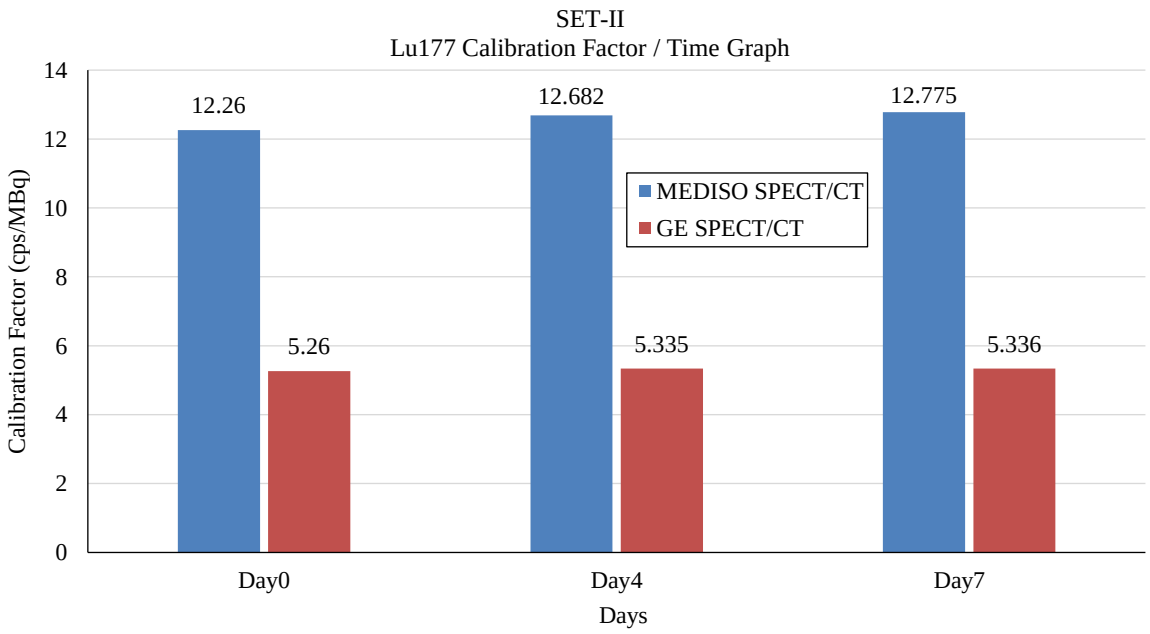


Figure 6. Analyses of calibration factor for each SPECT/CT in the SET-II study.

The comparison of CFs obtained from different experiments (SET-I study and SET-II study) with the same phantom and SPECT/CTs, the CF values in Figures 5 and 6 represent the following.

In the SET-I study, the CFs obtained from GE SPECT/CT at the three time points are represented as; 10.491 cps/MBq on Day 0, 4.338 cps/MBq on day 4 and 10.722 cps/MBqon Day 7. The calculated result shows that the CF remains approximately constant for two time points (Day 0 and Day 7) when the protocol was set for the whole body scan and CF was less on Day 4 when the protocol was changed to the head and neck scan. The CFs obtained from MEDISO SPECT/CT, at the three time points, are represented as; 5.986 cps/MBq on Day 0, 12.422 cps/MBq on Day 4, and 12.312 cps/MBq on Day 7 with the same protocol. The calculated result shows that the CF remains approximately constant for two time points (Day 4 and Day 7), but on Day 0, the CF is less; the reason was that the Lu-177 activity in the phantom was not distributed uniformly in the water solution.

To verify the reason for the decreased value of CF in the SET-I study, we again performed the study with a gap of 6 months for the same phantom and SPECT/CTs referred to as the SET-II study. In the SET-II study, the CF obtained from GE SPECT/CT, at the three time points, are 5.260 cps/MBq on Day 0, 5.335 cps/MBq on Day 4, and 5.336 cps/MBq on Day 7. The calculated result shows that the CF remains approximately constant for all the three time points (Day 0, Day 4, and Day 7) when the same head and neck scan protocol was set for the three days**.** The CF obtained from MEDISO SPECT/CT, at the three time points, are 12.260 cps/MBq on Day 0, 12.682 cps/MBq on Day 4, and 12.775 cps/MBq on Day 7 with the same protocol. The calculated result shows that the CF remains approximately constant for all the three time points (Day 0, Day 4, and Day 7). The Lu-177 activity in the phantom was distributed uniformly in the water solution.

DISCUSSION

For the accuracy of activity determination in the Lu-177 SPECT/CT scans of the phantom with uniform density, the imaging study was performed according to the recommendations in MIRD Pamphlets 23, 26 and ICRU report 96 [4, 14, 24]. The result shows that the CF for each SPECT/CT remains approximately constant at three time points in the SET-I study and SET-II study. In the SET-I study, the CF was obtained from GE SPECT/CT; for Day 4, CF was less due to the change in protocol for the whole body scan to the head and neck scan and the CF was obtained from MEDISO SPECT/CT, for Day 0 CF was less, the reason being that the activity in the phantom was not uniformly distributed. Hence, the results of our work strongly suggest that the CF also depends on the protocol used for the image acquisition and it should remain the same for all the time points for the phantom as well as for the patient image acquisition. The SET-I results suggest that to improve the accuracy of the calibration factor for the quantification of activity, proper care in the measurement of activity and preparation for uniform distribution of activity in phantom is required. Following these guidelines, the results in SET-II show constant values of CF at all the three time points both for GE and MEDISO SPECT/CT study.

We also performed a comparative study of the latest publications on the evaluation of calibration factor for Lu-177 SPECT/CT images of extended source Jaszczak phantom, which is shown in Table 5.

Table 5. A comparative study of the latest publications on the evaluation of calibration factor for Lu-177 SPECT/CT images of extended source Jaszczak phantom.

Tran-Gia et al. (2021) [20][a]	**Zhao et al. (2018) [21] (Siemens)**	**Uribe et al. (2017) [22] (Siemens)**	**Mehrotra et al. [this study] (GE, MEDISO)**
CF = 10–50 cps/MBq	CF = 10.10 cps/MBq	CF = 0.62 cpm/kBq	CF = 4.338–12.775 cps/MBq
[a]For 9 setups of SPECT/CT systems (Siemens, GE, Mediso) and different reconstruction software.			

Tran-Gia et al. [20] presented a study of nine setups of SPECT/CT systems (including Siemens, GE, and Mediso) with different reconstruction software using the same acquisition parameters. Jaszczak phantom data were acquired using standard reconstruction parameters for all nine setups with stable quantification observed for 2 subsets and 25 iterations and the setup-specific choices of scatter correction used for clinical imaging (mostly TEW). The CF values of Lu-177 for all nine setups ranged from around 10 to 50 cps/MBq. This study indicates that the CF directly depends on protocol, reconstruction settings/software and correction methodology.

Zhao et al. [21] performed a study with a cylindrical Jaszczak phantom filled with the uniform activity of Lu-177 Siemens SPECT/CT with CT-based attenuation correction and TEW scatter correction. The CF value calculated for 10 subsets and 6 iterations in the reconstructed image is 10.1 cps/MBq. This study suggested that the calibration factor value remains unchanged over a long period when the same type of SPECT/CT and the same acquisition protocols with TEW scatter correction along with attenuation correction are applied during image reconstruction.

Uribe et al. [22] evaluated the value of CF for Lu-177 as 0.62 cpm/kBq, with uniform activity in the Jaszczak phantom using Siemens SPECT/CT scans. The study was performed according to MIRD Pamphlets 23 and 26 recommendations.

Santoro et al. [29] performed a study with Lu-177 image data acquired by GE (NM/CT 670) SPECT/CT and compared the same data to calculate the CF using two software PLANET and Dosimetry Toolkit (DTK). The CF values were 67 ± 2.2 Bq.counts^{-1} with PLANET software and 5.60 ± 0.04 cps/MBq with Dosimetry Toolkit (DTK) software. They suggested that the values did not vary significantly over time. These CF values were used to determine the absorbed dose in the clinical dosimetry workflow.

Mora-Ramirez et al. [16] compared the CF values evaluated with five commercial dosimetry software from the GE SPECT/CT image acquisitions for Lu-177. The five software were: (1) Dosimetry Toolkit (DTK), (2) Hybrid Dosimetry Module (HDM), (3) STRATOS, (4) PLANET (PDOSE), and (5) SurePlan™ MRT. The CF values obtained were: 5.67 cps/MBq for DTK, 38.3×10^{-6} MBq/c for HDM, 38.3 Bq/intensity for STRATOS and 38.3 Bq/c for PDOSE and MRT using different image reconstruction algorithms. Their result suggested that (1) it is essential to calibrate SPECT/CT before the patient image acquisition and (2) for patient image acquisition, one should acquire the scans and reconstruct the images with corrections using the same data processing software in the same way as performed for extended calibration sources.

The finding of our study indicates that the value of CF for Lu-177 is in the same range between 4.338 to 12.775 cps/MBq for GE and MEDISO SPECT/CT image acquisition of cylindrical Jaszczak phantom filled with uniform activity, as compared with the other published work. It is recommended to acquire the reconstruction images and apply corrections for degrading factors in the same way as it is performed in the patient studies at different time points.

Corrections for Image Degrading Factors

ICRU Report 96 [24] suggests that activity quantification is considered to be the largest source of uncertainty in the dosimetry calculation; hence a careful selection of image acquisition parameters, image reconstruction methodology, correction for image degrading factors and evaluation of calibration factor for absolute quantification is of utmost importance.

- *Attenuation correction:* The emitted photons from Lu-177 undergo interaction in the tissue that results in the attenuation of the number of photons reaching the detector. CT-based attenuation corrections are generally faster and easy to acquire in hybrid SPECT/CT, where SPECT and CT are performed one after the other without changing the position of the phantom or patient. The

CT-based attenuation correction has better spatial resolution and good contrast due to lower noise. Our study used the low-dose CT acquisition data for the CT-based attenuation correction in image reconstruction [30, 31].

- *Scatter correction:* Photons get deflected with the patient tissues due to Compton or Rayleigh scattering, which degrades the image contrast and quantitative accuracy, the reason being that the scattered counts do not reflect the actual location of the photon emission within the patient. The TEW scatter correction method is widely used and easily implemented in clinical dosimetry workflow. In the present phantom-based study, the TEW method included scatter correction in the SPECT/CT image reconstruction. Regarding the camera calibration, our results show that when TEW corrections are applied, the CF values determined using the scans of the extended source are uniform, provided the Lu-177 activity in the phantom is uniformly distributed. TEW scatter correction method provides good accuracy for activity quantification.
- *Partial volume effect:* Partial volume effect (PVE) in SPECT/CT imaging is the blurring or spill-out and spill-in of the counts at the object's edges. Tran-Gia et al. [20] in their study, to calculate the calibration factor took the value of counts (C) in the reconstructed image of the cylindrical phantom within the VOI, corresponding to 120% of the height and 130% of the radius of the Jaszczak phantom for the correction of the partial volume effect. They selected the VOI slightly bigger than the actual size of the phantom to account for the spill-out counts at the edges of the phantom, specifically to reduce the count loss due to PVE. In our study, we have also taken VOI greater than the actual size of the phantom to correct the PVE counts at the edges. We have also observed that the counts are directly proportional to the volume of VOI; hence the value of VOI was kept constant for the measurement of counts (C) for the evaluation of the calibration factor in each set (SET-I and SET-II) for three time points. Currently, there is no widely accepted, well-validated method for correcting PVE for the SPECT/CT accurate activity quantification. Further efforts should be made to develop a better methodology for accurately measuring the partial volume effect in nuclear medicine data acquisition.
- *Dead-time correction:* Dead-time is the finite time interval to process each recorded photon or count and dead-time loss means that some counts are lost due to short dead-time. Hence, the dead-time related count losses should be corrected, resulting in image distortion [32]. In Lu-177 imaging, the dead-time effects are minimal due to the low yield of photons emitted in the decay of Lu-177. In our study, we have neglected the dead-time effect at three-time points as the amount of activity in the phantom was very small [21]. Uribe et al. [33] presented a study on the dead-time effect in quantifying Lu-177 activity for radionuclide therapy. They suggested that the dead-time correction should be based on count losses in the scatter correction photopeak window instead of the dead-time determination from the entire spectrum.

Our results indicate that the methods used in this study represent that the CF value determined using SPECT/CT scans purely corresponds to the camera efficiency for Lu-177 radioisotope, collimator, acquisition parameters and protocols, corrections for image degrading factors and reconstruction settings/software. Based on the results and observations from the CF study, we propose that it is essential to measure the activity in the calibration source carefully and that there should be frequent checks for the CF stability. The CF values obtained by SET-I and SET-II suggest that, under normal conditions, the CF will remain unchanged over a long period of time and for the same SPECT/CT (GE or MEDISO) with the same acquisition protocols, resulting in similar CF values.

CONCLUSION

While performing personalized dosimetry in radionuclide therapy, the absolute quantification of the CF is required to determine the absolute activity distribution in the patient's VOI. Hence same acquisition parameters and protocol should be used in the patient image acquisition. For quantitative imaging, accurately determining the SPECT/CT gamma camera CF is essential in translating the counts in the reconstructed images into the activity values. Our study supports that uniform activity distributed

over the entire phantom volume and reconstructed images obtained from the SPECT/CT with attenuation and scatter corrections are significant steps for accurately evaluating absorbed dose in the patient-specific PRRT study. The recommendations of MIRD Pamphlets 23, 26 and ICRU Report 96 were followed for data acquisition in the reconstruction of images for accurate activity quantification of CF. The calculated data suggest that the preparation of the calibration source and measurement of the activity are significant sources of error. Hence proper evaluation of the activity with the same protocol at all time points would improve the CF for the accuracy of dosimetry calculation. Based on these observations, we conclude that, for a personalized approach to obtaining the calibration factor for accurate activity quantification, the SPECT/CT images of the extended source phantom should mimic the actual patient at different time points for calculating time-activity curve fittings and absorbed dose in clinical dosimetry workflow.

Acknowledgments

The present study is a part of the research project (AIIMS Project Fellowship Code No. D-616/2022/RS), which is supported by the Department of Nuclear Medicine, All India Institute of Medical Sciences (AIIMS), Sri Aurobindo Marg, Ansari Nagar East, New Delhi, India 110029.

Funding

This research work is funded by the Women Scientist Scheme-A (WOS-A) under the Department of Science and Technology (DST), Ministry of Science and Technology, Government of India. (Grant Reference No. SR/WOS-A/PM-14/2019), for the Research project titled "Quantitative Analysis of Patient-Specific Internal Dosimetry Using Molecular Imaging Tools and softwares for Radionuclide Therapy", to Dr. Madhulika Mehrotra, as Women Scientist Fellow, under the mentorship of Dr. C.S. Bal, Professor and Head, as Project Investigator (PI), Department of Nuclear Medicine, AIIMS, New Delhi.

Conflict of Interest Statement

The authors declare no conflict of interest.

Author Contributions Statement

Conceptualization – MM, SB, CSB; literature search – MM; experimental studies – MM, SB, PM; data acquisition – MM, PM; data analysis – MM, SB, CSB; manuscript preparation – MM, SB, CSB; manuscript editing – SB, CSB; manuscript review – all authors have read and agreed to the published version of the manuscript.

Ethical Approval/or Institutional Review Board (IRB) Approval

The study protocol was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, New Delhi, India, Ref No. IEC-11/14.01.2022, approved on 17.01.2022.

REFERENCES

1. Ersahin D, Doddamane I, Cheng D. Targeted radionuclide therapy. Cancers (Basel). 2011; 3 (4): 3838–3855. doi: 10.3390/cancers3043838.
2. Radojewski P, Dumont R, Marincek N, Brunner P, Mäcke HR, Müller-Brand J, Briel M, Walter MA. Towards tailored radiopeptide therapy. Eur J Nucl Med Mol Imaging. 2015; 42 (8): 1231–1237. doi: 10.1007/s00259-015-3030-9.
3. Strigari L, Konijnenberg M, Chiesa C, Bardies M, Du Y, Gleisner KS, Lassmann M, Flux G. The evidence base for using internal dosimetry in the clinical practice of molecular radiotherapy. Eur J Nucl Med Mol Imaging. 2014; 41 (10): 1976–1988. doi: 10.1007/s00259-014-2824-5.
4. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjögreen-Gleisner K. MIRD pamphlet no. 26: joint EANM/MIRD guidelines for quantitative ^{177}Lu SPECT applied for dosimetry of radiopharmaceutical therapy. J Nucl Med. 2016; 57 (1): 151–162. doi: 10.2967/jnumed.115.159012.

5. Dash A, Russ Knapp FF, Pillai MRA. Targeted radionuclide therapy—an overview. Curr Radiopharm. 2013; 6 (3): 152–180. doi: 10.2174/18744710113066660023.
6. Santoro L, Mora-Ramirez E, Trauchessec D, Chouaf S, Eustache P, Pouget J-P, Kotzki P-O, Bardiès M, Deshayes E. Implementation of patient dosimetry in the clinical practice after targeted radiotherapy using [^{177}Lu-[DOTAo, Tyr3]-octreotate. EJNMMI Res. 2018; 8 (1): 103. doi: 10.1186/s13550-018-0459-4.
7. Kashyap R, Hofman MS, Michael M, Kong G, Akhurst T, Eu P, Zannino D, Hicks RJ. Favourable outcomes of ^{177}Lu-octreotate peptide receptor chemoradionuclide therapy in patients with FDG-avid neuroendocrine tumours. Eur J Nucl Med. 2015; 42 (2): 176–185. doi: 10.1007/s00259-014-2906-4.
8. Hennrich U, Kopka K. Lutathera®: the first FDA-and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. Pharmaceuticals (Basel). 2019; 12 (3): 114. doi: 10.3390/ph12030114.
9. Stabin M. The case for patient-specific dosimetry in radionuclide therapy. Cancer Biother Radiopharm. 2008; 23 (3): 273–284.(doi: 10.1089/cbr.2007.0445.
10. International Atomic Energy Agency. Coordinated Research Project. Dosimetry in molecular radiotherapy for personalized patient treatments. [Online]. Available at https://www.iaea.org/projects/crp/e23005 [Accessed on September 27, 2021].
11. Bardiès M, Gear JI. Scientific developments in imaging and dosimetry for molecular radiotherapy. Clin Oncol. 2021;33 (2): 117–124. doi: 10.1016/j.clon.2020.11.005.
12. Sanders JC, Kuwert T, Hornegger J, Ritt P. Quantitative SPECT/CT imaging of ^{177}Lu with in vivo validation in patients undergoing peptide receptor radionuclide therapy. Mol Imaging Biol. 2015; 17 (4): 585–593. doi: 10.1007/s11307-014-0806-4.
13. Lassmann M, Eberlein U, Tran-Gia J. Multicentre trials on standardised quantitative imaging and dosimetry for radionuclide therapies. Clin Oncol (R Coll Radiol). 2021; 33: 125–130. doi: 10.1016/j.clon.2020.11.008.
14. Dewaraja YK, Frey EC, Sgouros G, Brill AB, Roberson P, Zanzonico PB, Ljungberg M. MIRD pamphlet No. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. J Nucl Med. 2012; 53 (8): 1310–1325. doi: 10.2967/jnumed.111.100123.
15. Dewaraja Y, Frey E, Sunderland J, Uribe C. Dosimetry challenge. [Online]. Available at https://therapy.snmmi.org/SNMMI-THERAPY/Dosimetry_Challenge.aspx [Accessed on October 13, 2021].
16. Mora-Ramirez E, Santoro L, Cassol E, Ocampo-Ramos JC, Clayton N, Kayal G, Chouaf S, Trauchessec D, Pouget JP, Kotzki PO, Deshayes E. Comparison of commercial dosimetric software platforms in patients treated with ^{177}Lu-DOTATATE for peptide receptor radionuclide therapy. Med Phys. 2020; 47 (9): 4602–4615. doi: 10.1002/mp.14375.
17. Peters SMB, Meyer Viol SL, van der Werf NR, de Jong N, van Velden FHP, Meeuwis A, Konijnenberg MW, Gotthardt M, de Jong HWAM, Segbers M. Variability in lutetium-177 SPECT quantification between different state-of-the-art SPECT/CT systems. EJNMMI Phys. 2020; 7 (1): Article 9. doi: 10.1186/s40658-020-0278-3.
18. Beauregard J-M, Hofman MS, Pereira JM, Eu P, Hicks RJ. Quantitative ^{177}Lu SPECT (QSPECT) imaging using a commercially available SPECT/CT system. Cancer Imaging. 2011; 11 (1): 56–66. doi: 10.1102/1470-7330.2011.0012.
19. Seret A, Nguyen D, Bernard C. Quantitative capabilities of four state-of-the-art SPECT-CT cameras. EJNMMI Res. 2012; 2 (1): 45. doi: 10.1186/2191-219X-2-45.
20. Tran-Gia J, Denis-Bacelar AM, Ferreira KM, Robinson AP, Calvert N, Fenwick AJ, Finocchiaro D, Fioroni F, Grassi E, Heetun W, Jewitt SJ. A multicentre and multi-national evaluation of the accuracy of quantitative Lu-177 SPECT/CT imaging performed within the MRTDosimetry project. EJNMMI Phys. 2021;8: Article 55. doi: 10.1186/s40658-021-00397-0.
21. Zhao W, Esquinas PL, Hou X, Uribe CF, Gonzalez M, Beauregard JM, Dewaraja YK, Celler A. Determination of gamma camera calibration factors for quantitation of therapeutic radioisotopes. EJNMMI Phys. 2018; 5: Article 8. doi: 10.1186/s40658-018-0208-9.

22. Uribe CF, Esquinas PL, Tanguay J, Gonzalez M, Gaudin E, Beauregard JM, Celler A. Accuracy of ^{177}Lu activity quantification in SPECT imaging: a phantom study. EJNMMI Phys. 2017;4: Article 2. doi: 10.1186/s40658-016-0170-3.
23. Peters SM, van der Werf NR, Segbers M, van Velden FH, Wierts R, Blokland KA, Konijnenberg MW, Lazarenko SV, Visser EP, Gotthardt M. Towards standardization of absolute SPECT/CT quantification: a multi-center and multi-vendor phantom study. EJNMMI Phys. 2019; 6: Article 29. doi: 10.1186/s40658-019-0268-5.
24. Sgouros G, Bolch WE, Chiti A, Dewaraja YK, Emfietzoglou D, Hobbs RF, Konijnenberg M, Sjögreen-Gleisner K, Strigari L, Yen TC, Howell RW. ICRU REPORT 96, dosimetry-guided radiopharmaceutical therapy. J ICRU. 2021; 21 (1): 1–212. doi: 10.1177/14736691211060117.
25. De Nijs R, Lagerburg V, Klausen TL, Holm S. Improving quantitative dosimetry in ^{177}Lu-DOTATATE SPECT by energy window-based scatter corrections. Nucl Med Commun. 2014; 35 (5): 522–533. doi: 10.1097/MNM.0000000000000079.
26. D'Arienzo M, Cozzella ML, Fazio A, De Felice P, Iaccarino G, D'Andrea M, Ungania S, Cazzato M, Schmidt K, Kimiaei S, Strigari L. Quantitative ^{177}Lu SPECT imaging using advanced correction algorithms in non-reference geometry. Phys Med. 2016; 32 (12): 1745–1752. doi: 10.1016/j.ejmp.2016.09.014.
27. Ogawa K, Harata Y, Ichihara T, Kubo A, Hashimoto S. A practical method for position-dependent Compton-scatter correction in single photon emission CT. IEEE Trans Med Imaging. 1991; 10: 408–412. doi: 10.1109/42.97591.
28. Blinder S, Celler A, Wells RG, Thomson D, Harrop R. Experimental verification of 3D detector response compensation using the OSEM reconstruction method. IEEE Nucl Sci Symp Conf Rec. 2001; 4: 2174–2178. doi: 10.1109/NSSMIC.2001.1009254.
29. Santoro L, Pitalot L, Trauchessec D, Mora-Ramirez E, Kotzki PO, Bardiès M, Deshayes E. Clinical implementation of PLANET® Dose for dosimetric assessment after [^{177}Lu] Lu-DOTA-TATE: comparison with Dosimetry Toolkit® and OLINDA/EXM® V1. 0. EJNMMI Res. 2021; 11: Article 1. doi: 10.1186/s13550-020-00737-8.
30. Shcherbinin S, Piwowarska-Bilska H, Celler A, Birkenfeld B. Quantitative SPECT/CT reconstruction for ^{177}Lu and ^{177}Lu/^{90}Y targeted radionuclide therapies. Phys Med Biol. 2012; 57: 5733–5747. doi: 10.1088/0031-9155/57/18/5733.
31. Hippeläinen E, Tenhunen M, Mäenpää H, Sohlberg A. Quantitative accuracy of ^{177}Lu SPECT reconstruction using different compensation methods: phantom and patient studies. EJNMMI Res. 2016; 6 (1): Article 16. doi: 10.1186/s13550-016-0172-0.
32. Frezza A, Desport C, Uribe C, Zhao W, Celler A, Després P, Beauregard JM. Comprehensive SPECT/CT system characterization and calibration for ^{177}Lu quantitative SPECT (QSPECT) with dead-time correction. EJNMMI Phys. 2020; 7 (1): Article 10. doi: 10.1186/s40658-020-0275-6.
33. Uribe CF, Esquinas PL, Gonzalez M, Zhao W, Tanguay J, Celler A. Dead-time effects in quantification of ^{177}Lu activity for radionuclide therapy. EJNMMI Phys. 2018; 5: Article 2. doi: 10.1186/s40658-017-0202-7.

