The comparison of serial SPECT-CT imaging to estimate absorbed dose to the organ at risk from peptide receptor radionuclide therapy dosimetry

Original Article

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ABSTRACT

Introduction: In Peptide Receptor Radionuclide Therapy (PRRT), the administration of radionuclide such as Lu-177 label with a pharmaceutical agent useful to destroy the lesion. The amount of Lu-177 radioactivity administered to the patients is still not standardize and generally not more than 7.4 GBq per session due to the patient's safety issues. The first cycle of Lu-177 is an excellent technique to estimate radionuclide uptake for organs at risk. This study aims to simplify five SPECT-CT scanning points into less scanning points to estimate absorbed dose to the organ at risk.

Methods: Ten patients who have neuroendocrine tumors enrolled in ^{177}Lu-Dotatate therapy dosimetry. The serial SPECT-CT done after 2, 4, 24, 48 and 72 hours to acquired time disintegration for organ at risk. Partik's categorical grading criteria is relevantly used in this study to convert the numeric value of Lin's concordance coefficient into an ordinal scale.

Results: Our current result demonstrated an excellent agreement between three and five scanning with LSA exponential fit method. These excellent results presented for kidney, liver and spleen. However, the bladder shows poor results due to the urinary system.

Conclusion: Three data point of SPECT-CT images is the best option to estimate absorbed dose to the lesion and organ at risk for ^{177}Lu-Dotatate dosimetry technique.

Key words: ^{177}Lu-Dotatate; Dosimetry; SPECT-CT

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INTRODUCTION

Peptide Receptor Radionuclide (PRRT) is an excellent therapy to treat Neuroendocrine Tumor (NET) recently. In PRRT, the administration of ^{177}Lu-Dotatate was done serially up to five cycles within four to six months interval is used to destroy the cancerous cells and at the same time to avoid the toxicities issues to the organ at risk. The amount of ^{177}Lu-Dotatate radioactivity administered to the patients equal or less than 7.4 GBq per session due to the patient's safety issues as a practice is most of the nuclear medicine center [1, 2]. Several researchers had introduced several internal dosimetry technique assessments to estimate absorbed dose to the organ at risk [3, 4]. The first cycle of PRRT treatment with Lu-177 is the best time to determined Lu-177 absorbed dose to the organ at risk [5]. In this therapy, kidney is the most critical organ compared with others and the maximum tolerates absorbed dose to this organ is between 23-40 Gy based on a previous studies [6, 7]. Others organs such as liver, spleen and bladder also include in this study due to the photon cross radiation to the kidneys. As suggested by previous publications, the kidney absorbed dose assessment only can be done with multiple whole-body SPECT-CT scanning [8]. The most recommended serial SPECT-CT scanning done every 2, 24, 48, and 96 h after intravenous administration of Lu-177. However, several researchers had proposed other methods to estimate absorbed dose for organ at risk [9–11]. This study aims to quantify the agreement (r) several sets of data five sequential scanning time points as reference and other sequential scanning time points.

METHODS

Ten patients who have NETs enrolled in ^{177}Lu-Dotatate therapy dosimetry in our center since 2019 until March 2020. All patients signed written informed consent. Ten suitable patients were selected by Nuclear Medicine Physicians to undergo the PRRT dosimetry procedure as followed with the joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumor [10]. The SPECT-CT ^{177}Lu-Dotatate therapy dosimetry procedure done at the first cycle of post ^{177}Lu-Dotatate. The serial SPECT-CT done after 2, 4, 24, 48 and 72 hours to acquired time disintegration for organ at risk such as kidney. Our SPECT sensitivity is 0.011884566 kcps/Mbq and voxel size used in this study is 0.104 ml. Details of the calibration had been mentioned before from previous study [12].

The SPECT data were acquired using automatic body contouring with a total of 48 angular views at steps of 6° (15 s/projections) and pixel size are 4.66 x 4.66 mm, zoom is 1.0. SPECT data acquired for three-bed positions covering from the abdomen to chest region. Low-dose CT imaging was performed with parameter of 120 kVp for tube voltage and 20 mA for tube current. Parameters are followed according to our department's clinical standard procedure for all imaging sequential scanning time points in this research. The same CT image also used for the SPECT attenuation correction and as well for image registration of different scanning time points. CT data reconstructed with iterative method algorithm with pixel size 2.00 x 2.00 mm and a slice thickness of 2.75 mm. All the SPECT images analyses with MIM Software 6.9.4 (trial version). In order to quantify the agreement between the five scanning time points as reference with other scanning time points, Six different combinations of SPECT-CT scanning time points were used to fit the curve in estimating the number of disintegrations occurred in a source organ such as liver, kidney, spleen and bladder as shown in Table 1.

The five agreements were compared to determine the best agreement between references with other groups, as shown in Table 2.

Table 1: SPECT-CT scanning data point.

Group	SPECT Acquisitions post Lu177 (hour)
Reference	2, 4, 24,48 and 72
1	2, 24 and 72
2	2 and 72
3	2 and 48
4	24 and 72
5	4 and 72

Table 2: SPECT-CT Data SETs to evaluate the agreement between groups.

SET	Group
A	Reference and Group 2
B	Reference and Group 3
C	Reference and Group 4
D	Reference and Group 5
E	Reference and Group 6

Partik's categorical grading criteria is the best technique to be applied in this study for converting the numeric value of Lin's concordance coefficient into an ordinal scale [13]. The criteria designate values of LCC > 0.95 as 'excellent', > 0.90 'very good', > 0.80 'fairly good', > 0.70 'middling/satisfactory' > 0.60 'mediocre', > 0.50 'poor' and 0.50 as 'unacceptable'[14]. The steps to find an agreement between Reference and several groups were summarized in the flowchart shown in Figure 1.

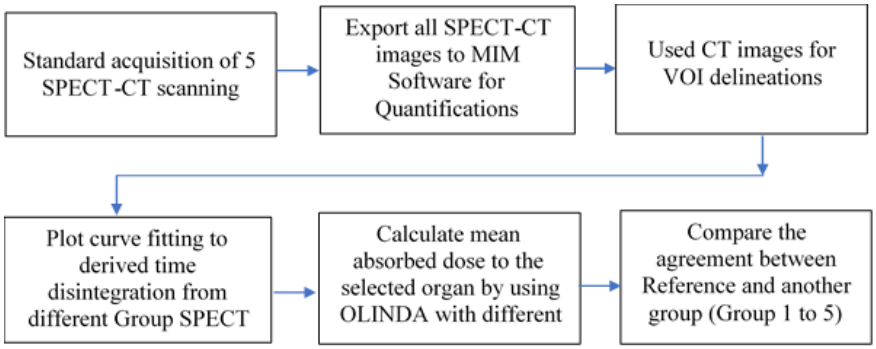

Fig 1. The summary of the steps performed to determine the agreements between data set.

Table 3: Patients organ volume and Reference Time Disintegrations.

Patients Identifications	Organ Weight (g)				Time Disintegrations (h)			
	Kidneys	spleen	Liver	Bladder	Kidneys	spleen	Liver	Bladder
Pt 01	275	69	1745	431	1.12	1.61	13.30	1.55
Pt 02	370	280	1552	141	0.89	0.61	6.86	0.52
Pt 03	425	181	1669	141	0.58	0.11	2.06	0.53
Pt 04	195	94	2404	223	2.51	2.13	2.17	1.13
Pt 05	223	94	2404	48	1.52	0.33	3.08	0.16
Pt 06	249	96	1504	74	1.46	0.18	5.77	0.21
Pt 07	276	70	1281	215	0.09	0.02	2.33	0.57
Pt 08	275	72	1220	126	0.56	0.08	1.54	0.74
Pt 09	338	245	2566	158	1.52	0.03	7.67	0.06
Pt 10	338	96	1504	74	5.23	0.34	21.60	1.46

RESULTS

The absorbed dose estimation expressed in Gy/GBq of Lu-177 and mean administered activity of ^{177}Lu-Dotatate was 7,489 ± 259 MBq. The absorbed dose for organ in this study is based on the number of disintegrations occurring in a source organ such as kidney, liver, spleen and bladder. Table 3 presented disintegration time for kidneys, spleen liver and bladder are between 0.09 to 5.24, 0.04 to 2.09, 1.74 to 22.60 and 0.05 to 1.75 hour, respectively, for all patients. Figure 2 demonstrated SET A consist of Group 1 found the excellent agreement between Reference, especially kidney 0.9913, spleen 0.9650, liver 0.9907 and bladder 0.9946. Other SETs presented between 0.8803 to 0.9677, 0.9364 to 0.9767, 0.9046 to 99.39 and 0.4761 to 0.9918 agreement for kidney, spleen, liver and bladder. Refer to Figure 2, SET A shown excellent agreement between Reference and Group 1 that were consistent result between both three and five data point for all organ. SET B to SET E presented less agreement between all groups compare SET A. The lower agreement for disintegration time shown cause absorbed doses less accurate and less consistent result between both other group scanning time point with five data point for all organ.

DISCUSSION

The number of disintegrations occurring in a source organ estimations lesion is a fundamental parameter to estimate absorbed dose. Generally, the accuracy of the number of disintegrations occurring in a source organ very crucial to estimate the accurate result, as shown in Equation 1. The organ weight obtained from CT images by apply organ volume segmentation to the selected organ such as kidney, spleen and bladder. After the injection of ^{177}Lu-Dotatate to the patients, that radiopharmaceutical will move to the peptide receptor to the respective organ as described in other publications [15]. The SPECT segmentation method is less accurate than with PET radiopharmaceutical due to the physical properties form the radionuclide. Although, Philips Brightview gamma camera designed with used low dose CT, those images corrected with Iterative reconstructed algorithm used for attenuation correction with the SPECT images.

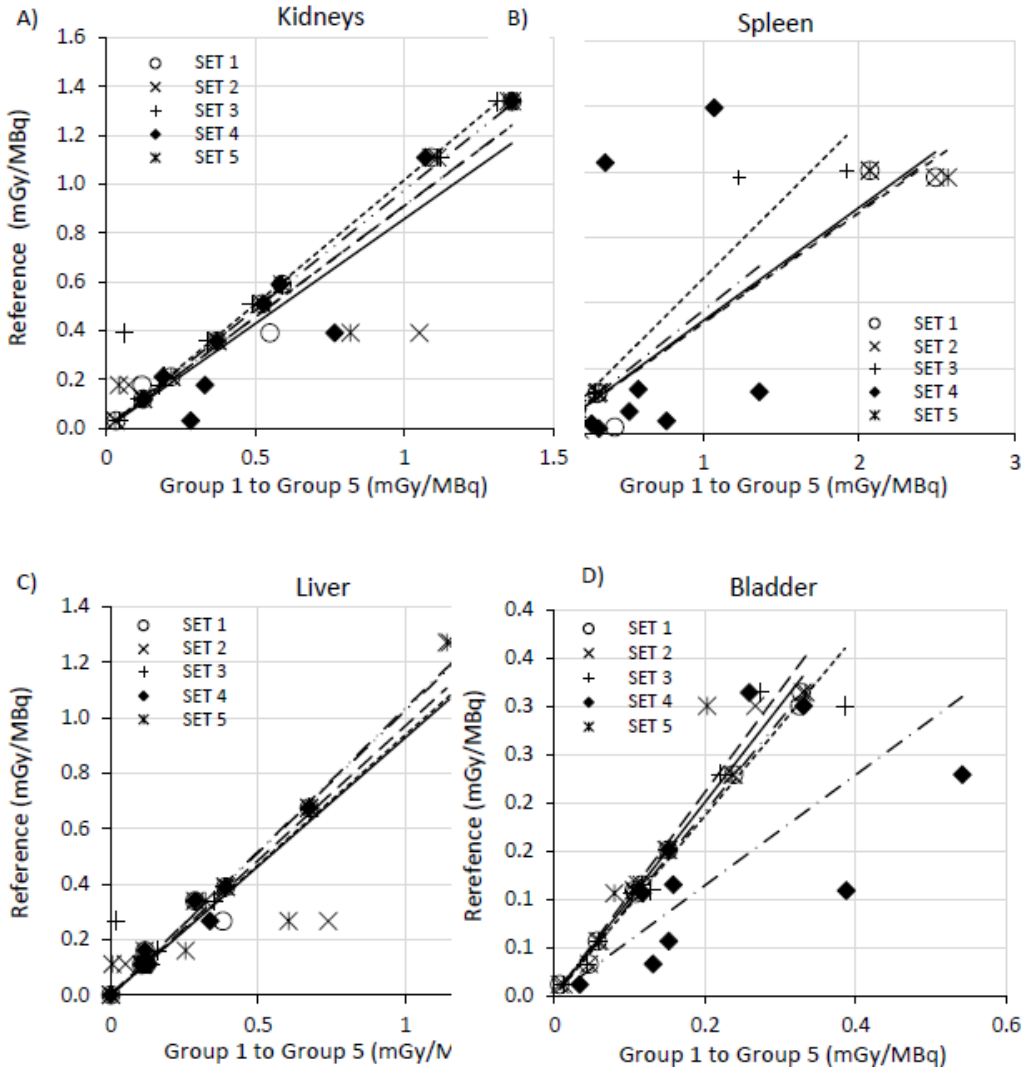

Figure 2. a) kidneys, b) spleen, c) liver and d) bladder agreements for all SETs.

This technique gives consistency result. ASTONISH Reconstruction introduced by PHILIP was good image restoration process to enhance the image resolution for SPECT. These techniques by using the blind deconvolution technique currently the most widely used iterative reconstruction technique and provides better image quality and consistent value. The organ volume segmentation from CT images will be transfer and fused with serial SPECT images. The SPECT imaging protocol in this study similar to another center [16] which no scatter photon correction applied to the SPECT acquisitions. The absorbed dose to whole organs, tissue subregions, voxelated tissue structures, and individual cellular compartments from internally deposited radionuclides define below:

$$\bar{D}_{[Gy]}(r_t) = \sum_{r_s} \tilde{A}_{r_s} * S_{[Gy]}(r_t \rightarrow r_s) \quad (1)$$

Where $\bar{D}$ referred to absorbed dose at the target organ, r_t and r_s refer target and source organ, $\tilde{A}_{r_s}$ refer to cumulated activity at target organ and $S_{[Gy]}(r_t \rightarrow r_s)$ the is the mean absorbed dose per cumulated activity form r_s to r_t. $\tilde{A}_{r_s}$ is very critical to estimate dose to the essential organ. In this study, the cumulated activity $\tilde{A}_{r_s}$ derived directly by mathematically measuring the area under the time-activity curve that plots the effective disappearance of activity in an organ, or the integral may approximate by standard methods such as the trapezoidal rule. According to [17] the most common practice to an estimated number of disintegrations occurring in a source organ are by using Least Squares Analysis (LSA) method is an excellent alternative to minimize the square error between scanning point. The curves represented by mathematical formula directly integrated. However, the less scanning cycle might probably produce deviation from the actual result, and not suitable with

trapezoidal rule. Our current presented result also similar to another study before [18], LAS technique is a straight forward method and easy to implement. The reduction of data points possible because the combination of biological and physical half-life would create the uniform effective disappearing activity to the normal organ. Most of the uptake in organs predicted according to the definitive assessment of the said level of concordance using Partik's grading schema. Our current result Figure 2 demonstrated the Group 1 found the excellent agreement between Reference compare with other SETs. The LAS method useful to estimate the optimum time disintegration for all organ at risk. The later scan is crucial to determine kidney absorbed dose and single scanning time point method using LAS method with, monoexponentially approached (48–72 hour for kidneys) produces <10% deviation and can be considered [19]. In some situation mono exponential can be replaced with bi or tri exponential to fit curve fitting. The similar result also found by other researchers, and they claimed a group of three SPECT scanning (2, 24 or 48 and last measurement 72 hour) enough to represent the excellent result of MTA [20] for I131 therapy. The I-131 simplification dosimetry approach would be an excellent example to be considered in ^{177}Lu-Dotatate dosimetry approached. Agreed with [19] all groups fulfilled this requirement except Group 4. The most accurate method to estimated absorbed dose to organ at risk by using delayed scanning at times beyond 72 hour as suggested by [21], but the patient would discomfort with this suggestion. The 24 hour is the best choice of many investigators to focus slower phase which starts after 24 hour, because this takes more than 70% of total time disintegration at the critical organ as pointed out by previous researcher [22]. The effective half life is the

$$T_{ef} = \frac{1}{T_{phy}} + \frac{1}{T_{bio}} \qquad (2)$$

T_{phy} is the radionuclide half-life and T_{bio} is the organ kinetic into half amount and T_{ef} effective half-life. The uniform activity disappearance in the target organ is an advantage to omit the 48 hour scanning data point. Group 2 to group 5 only used 2 data points, hence, we had difficulties in estimating the reliable disintegration of time result because of not enough data point to fit in to the graph and it was not suitable for LSA technique due to unavoidable errors. The late data point is very important to determine the accurate radionuclide kinetic distributions [8]. The current technique gives an option to the patients had difficulties in undergoing repeated SPECT CT scanning procedure from five-time into three time for every procedure. Personnel handle the patients undergo SPECT-CT scanning would probably receive low exposure from the patients by reduction of several scanning procedures. The low CT very challenging to delineate organ volume segmentation, especially spleen. The CT form high dose will help to delineate the accurate segmentation. Different patient positioning (e.g. SPECT imaged with arms stretched upwards and whole-body imaged with arms next to the body) may have led to an internal shift of organs and tumors as reported by [16]. This issue solved by using patients' vacuum bag to use immobilization of patients during SPECT-CT acquisition to avoid a mispositioning organs and tumors. The CT-based segmentation resulted in an almost perfect agreement of the organ definitions with a similar renal dose by using MIM box based assisted alignment features.

CONCLUSION

Three data point of SPECT-CT images is the best option to estimate absorbed dose to the lesion and organ at risk for ^{177}Lu-Dotatate dosimetry technique. This option also will ensure patient are more comfortable due to the less imaging procedure. Hybrid imaging approaches combining SPECT-CT provide a compromise between accuracy and user-friendliness. Further prospective studies are warranted to assess the benefits of ^{177}Lu-Dotatate post dosimetry for the individual patient and, in particular, the patient outcome.

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