A dosimetric comparison of systemic peptide receptor radionuclide therapy and intra-arterial peptide receptor radionuclide therapy in patients with liver dominant gastroenteropancreatic neuroendocrine tumours

Original article

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A dosimetric comparison of systemic peptide receptor radionuclide therapy and intra-arterial peptide receptor radionuclide therapy in patients with liver dominant gastroenteropancreatic neuroendocrine tumours

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Objectives **Intra-arterial radionuclide therapy (IART) treatment allows direct delivery of ^{177}Lu-DOTATATE to the overexpressed somatostatin-positive neuroendocrine liver metastases, which led to higher tumour concentration compared with systemic radionuclide therapy (SRT). The aim was to evaluate and compare the absorbed doses of both IART and SRT to organs and hepatic metastatic sites.**

Methods **A total of 48 patients received SRT and IART. In SRT, activity was administered intravenously, whereas in IART, activity was administered directly into hepatic arteries. The sequential whole-body images were acquired at 2, 4, 24, 72 and 160 h. The reconstructed whole-body planar and single-photon emission computed tomography-computed tomography images were processed using the Dosimetry Toolkit for the estimation of normalized cumulated activity in the organs and tumour lesions. The absorbed dose was computed using OLINDA EXM 2.0 software.**

Results **The median absorbed dose (mGy/MBq) of kidneys and spleen in IART was compared with SRT and found to be decreased by 30.7% ($P = 0.03$) and 37.5% ($P = 0.08$), whereas it was found to be increased by 40% ($P = 0.26$) and 8.1% ($P = 0.28$) in the liver and lungs. The median dose (mGy/MBq) of tumours determined in IART was found to be increased by 62.2% ($P = 0.04$).**

Conclusion **IART with ^{177}Lu-DOTATATE significantly increases tumour dose while reducing overall systemic toxicity in comparison to SRT treatment. After considering the maximum tolerance limit of kidneys in peptide receptor radionuclide therapy, the number of treatment cycles and injected activity can be optimized further with IART for better response and survival.** ***Nucl Med Commun*** **44: 585–595**

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Keywords: intra-arterial radionuclide therapy, ^{177}Lu-DOTATATE, organ dosimetry, peptide receptor radionuclide therapy, systemic radionuclide therapy

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Introduction

Neuroendocrine tumours (NETs) are usually considered rare tumours but their incidence is increasing over time. Somatostatin receptors (SSTR) are found on the surface of normal tissues, including various organs, such as brain, gastrointestinal tract and a variety of cancerous cells, such as NETs, lymphoma, etc. A very important and crucial characteristic of the transformation of a normal to a cancerous cell is the overexpression of already existing SSTR receptors. Peptide receptor radionuclide therapy (PRRT) with (177) lutetium-[DOTA(0),Tyr(3)] octreotate (^{177}Lu-DOTATATE) is a promising treatment option against the overexpressed SSTR-positive inoperable and metastatic gastrointestinal NETs [1]. For several years, PRRT treatment has been available for patients [2–5].

The liver is the most common site of metastases in gastroenteropancreatic NETs (GEP-NETs) and treatment options for extensive hepatic metastatic disease are often limited [6,7]. The conventional treatment options for the metastatic hepatic disease include transarterial chemoembolization, radiofrequency ablation and selective internal radiotherapy. Another standard and popular treatment option is systemic radionuclide therapy (SRT) with ^{177}Lu-DOTATATE which substantially increases progression-free survival (PFS) and overall survival (OS) with minimal side effects in advanced-stage NET patients [8,9]; however, studies have shown lower PFS in patients with hepatic metastases post ^{177}Lu-DOTATATE SRT treatment [10,11]. The liver lesions larger in size are significantly associated with a worse PFS after ^{177}Lu-DOTATATE SRT treatment

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Table 1 Clinical data of patients with (systemic radionuclide therapy) and (intra-arterial radionuclide therapy) peptide receptor radionuclide therapy

	All $n = 48$	SRT ($n = 27$)	IART ($n = 21$)	P value
Male/female	33/15	16/11	17/4	–
Age (years)	54.593 ± 13.88	50.13 ± 13.41	60.21 ± 11.37	0.06
Height (cm)	163.5 ± 10.61	165.2 ± 9.71	161.5 ± 11.31	0.39
Weight (kg)	60.25 ± 13.50	61.53 ± 16.08	58.66 ± 9.06	0.14
DTPA GFR (ml/min)	82 ± 16.32	85 ± 14.11	79 ± 17.1	0.25
Extrahepatic disease	33	18	15	–
Intrahepatic disease	15	5	10	–
Creatinine and haematology level				
Creatinine (mg/dl)	0.94	1.07	0.91	0.14
WBC (per µl)	7537.2	8120.6	7362.7	0.08
Neutrophil (per µl)	5173.5	5483.2	5122.8	0.11
Platelet ($\times 10^6$/l)	290.6	299.3	287.4	0.16
Tumour grading				
Ki-67 G1 (<3%)	8	5	3	–
Ki-67 G2 (3–20%)	38	17	21	–
Ki-67 G3 (>20%)	2	1	1	–
Administered activity (GBq)	7.24 ± 0.38	7.28 ± 0.23	7.22 ± 0.44	0.6

P = significance of difference between patient parameters.
DTPA GFR, diethylenetriaminepentaacetic acid glomerular filtration rate; IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy; WBC, white blood cell.

Table 2 Inclusion and exclusion criteria of study

Inclusion criteria	Exclusion criteria
Consent must be given in writing by the patients	Hb < 5.5 mmol/l
A life expectancy of 6 months or more	High mitotic count or Ki-67 labelling index
A histologically proven neuroendocrine tumour that is inoperable and indicated for ^{177}Lu-DOTATATE	GFR < 50 ml/min
Patients aged 18 years or older	Higher serum bilirubin
Confirmation of somatostatin receptors in the target lesions	WBC < 3000/µl
Positive lesions on 68Ga-DOTANOC imaging in liver lobes	Platelet < 150 × 10^9/l
Excessive liver metastases	Creatinine > 1.5 mg/dl
Women of childbearing age with negative pregnancy test	No previous history of external beam radiation therapy, radio or chemoembolization to the liver

GFR, glomerular filtration rate; Hb, haemoglobin; WBC, white blood cells.

[12,13]. In SRT, a considerable amount of the radioactive dose is dissipated within the systemic circulation due to intravenous administration of radionuclides for therapy and therefore only a reduced amount of the dose reaches the target sites. A few dosimetry studies have also demonstrated toxicity to bone marrow and kidneys from ^{177}Lu-DOTATATE SRT treatment due to systemic and off-target exposure [14,15].

On the other hand, intra-arterial radionuclide therapy (IART) treatment allows direct delivery of ^{177}Lu-DOTATATE to the tumour sites within the liver via intra-arterial cannulation of the hepatic artery [16]. Previous studies have demonstrated that intra-arterial administration led to higher tumour concentration compared with intravenous administration [17,18]. Due to the fact of the first-pass effect, which results due to the higher affinity of SSTR on GEP-NET, a higher percentage of DOTATATE is expected to reach the metastatic hepatic sites which subsequently delivers a higher absorbed dose [6]. IART also minimizes the bioavailability of the DOTATATE in systemic circulation and thus reducing the toxicity to the tissues and organs [19]. Previous studies have shown that intra-arterial administration led to higher tumour concentration, however, it remains unclear whether Intra-arterial administration may reduce systemic toxicity compared with intravenous administration [13,16].

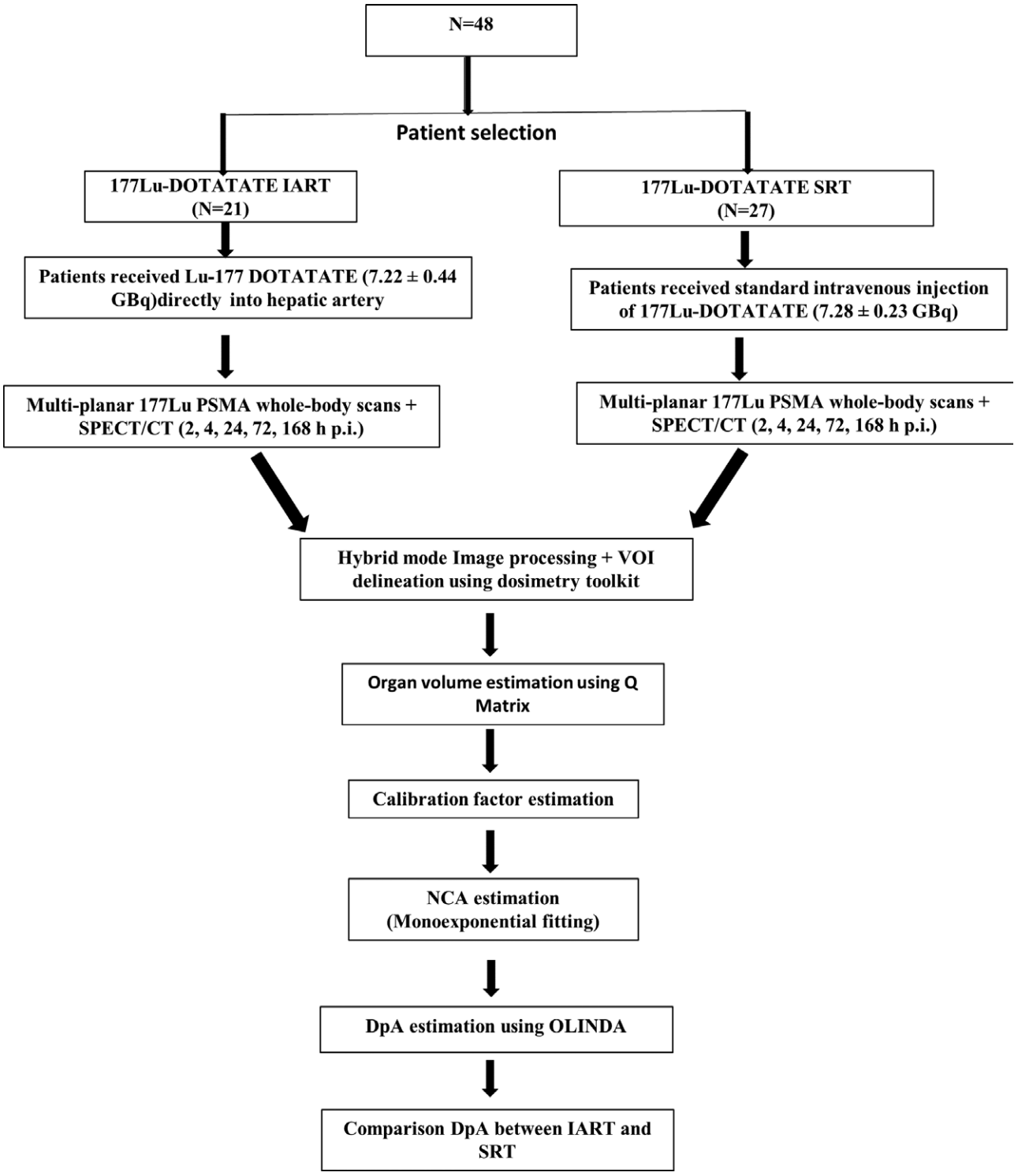
IART treatment with ^{177}Lu-DOTATATE appears to deliver more doses to metastatic hepatic sites, but not many studies have been performed from a dosimetry perspective to evaluate the efficacy of IART treatment compared with SRT treatment. It is also challenging to increase the number of treatment cycles and maximum administered activity in ^{177}Lu-DOTATATE SRT treatment. The present study was performed to evaluate and compare the absorbed doses of both ^{177}Lu-DOTATATE IART and SRT treatment to organs and hepatic metastatic sites in patients with GEP-NET.

Materials and methods

Patient selection

For this prospective study, we included 48 patients (54.593 ± 13.88 years) who received SRT treatment (n = 27) by intravenous injection and IART treatment (n = 21) by intra-arterial injection for the treatment of progressive GEP-NETs. This was a prospective study approved by the institutional review board for patients having biopsy-proven well differentiated GEP-NET liver metastases and informed consent was obtained from all the patients before participation. The detailed patient characteristics and clinical data of both groups of patients are mentioned in Table 1. Patients with gastric, enteric or pancreatic-originated NET with liver metastases and SSTR-positive disease were eligible for

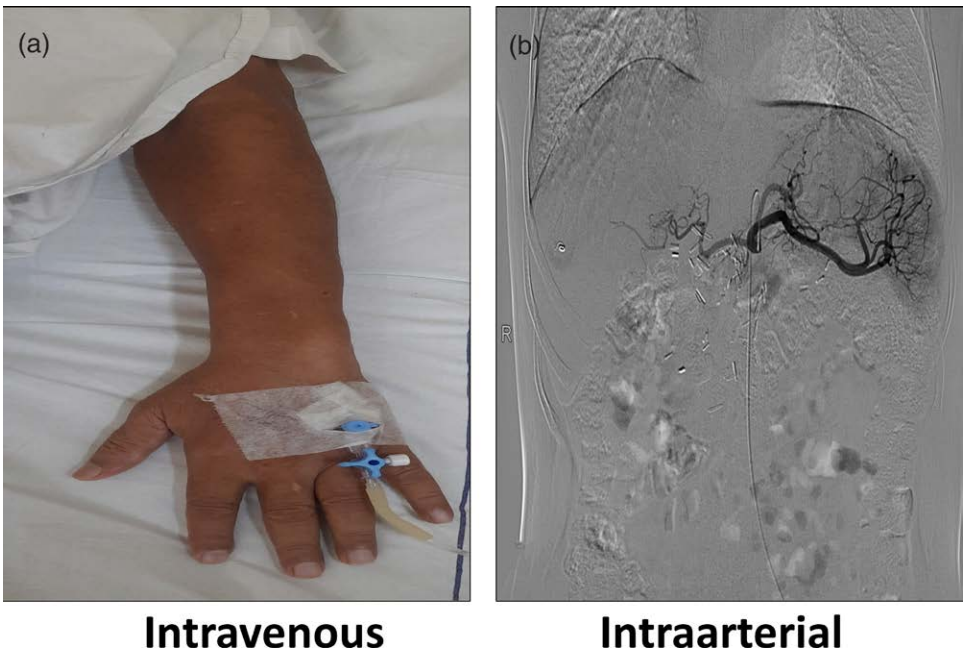
Fig. 1



Flow chart of study.

inclusion. The detailed inclusion and exclusion criteria of the study are mentioned in Table 2. Before starting the therapeutic procedure, antiemetics were given to the patients to avoid nausea or vomiting. All patients were prepared as described in the standard international guidelines before undergoing SRT and IART PRRT treatment [4]. ^{177}Lu-DOTATATE having radio chemical purity of more than 98% was procured in a

Fig. 2



PRRT treatment using two different methods. (a) Intravenous administration which leads to the systemic circulation of 177Lu-DOTATATE (SRT). (b) Intra-arterial administration of 177Lu-DOTATATE in the hepatic artery (IART). IART, intra-arterial radionuclide therapy; PRRT, peptide receptor radionuclide therapy; SRT, systemic radionuclide therapy.

ready-to-use form for the treatment of both groups of patients. The detailed flow chart of the study is mentioned in Fig. 1.

Dose administration and treatment with systemic radionuclide therapy

Mean activity of 7.28 ± 0.23 GBq ^{177}Lu-DOTATATE was administered intravenously by infusion along with amino acids diluted with normal saline over 30 min (Fig. 2a). The infusion of amino acid and saline was started 30 min before the administration of activity. Patients were infused with amino acids for a total of 4 h.

Dose administration and treatment with intra-arterial radionuclide therapy

In IART treatment, a slow injection of 10 ml ^{177}Lu-DOTATATE (7.22 ± 0.44 GBq) was administered into the right or left hepatic arteries through an intra-arterial microcatheter over 30 min based on the tumour burden within the respective liver lobes (Fig. 2b). A femoral or radial approach was used to catheterize the selected hepatic arteries during the angiography procedure. Before the administration of the activity, an infusion of amino acids was initiated. An intra-arterial catheter would be inserted in right and left hepatic arteries of patients with bi-lobar disease, and two infusions would be administered for the same. During administration, all the syringes were shielded with a lead-lined syringe shield. The above procedure was performed in the Interventional radiology department. Patients were infused with amino acids for a total of 4 h.

Image acquisition post systemic radionuclide therapy and intra-arterial radionuclide therapy treatment

Following treatment, sequential planar whole-body scans were acquired at approximately 2, 4, 24, 72 and 160 h and a single single-photon emission computed tomography (SPECT)/computed tomography (CT) imaging of the thorax and abdomen was performed 24 h (±4 h) post-injection using the GE Discovery 670 Pro SPECT-CT system (GE Healthcare, Haifa, Israel). The acquisition time for each planar imaging time point was 20–25 min. The details of the acquisition parameters are mentioned in Table 3.

Calibration factor estimation

The calibration factor of the system was calculated as per the protocol specified by the vendor to convert region of interest or volume of interest (VOI) counts to activity. For this, a known activity (100 MBq) of ^{177}Lu was taken in a petri dish and counts were obtained independently from each detector. The sensitivity of the SPECT/CT system for 177Lu was estimated as follows:

$$Sensitivity(cps/MBq) = \frac{c/t}{A/d} \quad (1)$$

where c = number of counts per pixel, t = total acquisition time, A = activity in the petri dish (MBq) and d = decay

Table 3 Image acquisition parameters

Collimator and energy window	Collimator selection	MEGP
	Energy window and scatter window	113 keV ± 10% and 208 keV ± 10% (79.1 keV-101.7 keV, 124.3 keV-146.9 keV and 146 keV-187.3 keV)
Planar	Exposure time per pixel (sec)	250
	Zoom	1
	Matrix size	256 × 1024
	Image time post-injection (h)	2, 4, 24, 72 and 160
	Pixel size (mm)	2.2
SPECT	number of beds	2
	Acquisition mode	Step and shoot
	Matrix size	128 × 128
	No of projections	60
	Time per view (s)	20
	Angular increment (degree)	6
	Reconstruction (iterations and subsets)	OSEM(2 and 10)
	Image time post-injection (h)	24
	Voxel size (mm^3)	1.8
CT	Tube voltage kVp	120
	Tube current mAs	80
	Slice thickness (mm)	3.75
	Tube rotation time (s)	0.8
	Matrix size	512×512
	Pitch	1.37
	Reconstruction	ASiR
	Voxel size (mm^3)	0.75

ASiR, adaptive statistical iterative reconstruction; CT, computed tomography; MEGP, medium energy general purpose; OSEM, ordered subset expectation maximization; SPECT, single-photon emission computed tomography.

correction factor. These results were used by dosimetry toolkit software to estimate the activity at each imaging time point.

Image processing and normalized cumulated activity estimation

For reconstruction and registration of the whole-body planar and SPECT images of both SRT and IART treatment groups, the extended dosimetry toolkit package was used to reconstruct the data. During reconstruction, planar and SPECT data were converted into similar pixel and matrix sizes (256 × 256). SPECT image reconstruction involved correction of motion, scatter, attenuation and resolution recovery. The reconstructed whole-body planar and SPECT-CT images were processed using the GE Dosimetry Toolkit (DTK) for the estimation of normalized cumulated activity (NCA) in the kidneys, spleen, liver, lungs and tumour lesions. First, organ delineation was performed on the 3D SPECT/CT images by using the semi-automatic VOI segmentation tool over the kidneys, spleen, liver, lung and tumour lesions. In the case of metastatic liver lesions, each tumour VOI within the liver was delineated first, which was then subtracted from the healthy liver VOI. After the organs and lesions were defined, the 3D processed data was projected over the 2D whole-body planar images to subtract and correct the superimposed regions on organ ROIs. In all planar images, overlapping organ volumes were automatically removed. In SPECT VOIs, the mean uniformly distributed radioactivity concentration was used for the activity correction from the subtracted volume of the organs. To convert planar data into SPECT activity concentration at 24 h, the following formula was used:

$$A(t) = \frac{A_{PL}(t)}{A_{PL}(T_s)} \times \frac{A_S(T_s)}{R.C.} \quad (2)$$

where $A(t)$ = activity concentration at time t, $A_{PL}(t)$ = activity concentration in planar images at time t, A_S: activity concentration in SPECT image, T_s = time point at which SPECT image was obtained (24 h post-injection), $A_{PL}(T_S)$ = planar activity concentration acquired at time T_S (24 h post-injection), R.C. = SPECT VOI recovery coefficient.

Further, the imaging data set was processed for the NCA estimation. Parameters used to generate the time-activity curves (TAC) for each organ and tumour were patient height and weight, tracer information and system sensitivity. All TACs were fitted mono-exponentially to estimate NCA. The output of DTK represents the activity as a percentage of the injected dose within the organ and tumour lesions for each imaging time point. The percentage injected dose was calculated using the following formula:

$$\%ID = \frac{A_{source\ organ}}{A_0} \times 100 \quad (3)$$

$$A_{source\ organ} = \frac{counts\ per\ minute(cpm)}{sensitivity\ of\ system\ (cps/MBq)} \quad (4)$$

Where $A_{source\ organ}$ = activity concentration in the source organ and A_0 = injected activity (MBq).

The activity concentrations at each time point were fitted using the monoexponential fitting function for the estimation of cumulated activity (Ã). Subsequently, the NCA was given by:

$$\text{NCA (MBq.h/ MBq)} = \frac{\tilde{\mathbf{A}}}{A_0} \quad (5)$$

Similarly, the remainder body NCA was estimated as the difference between NCA in the total body and the sum of NCA in the kidneys, spleen, liver, lungs and tumour lesions. The volume of each organ and tumour was obtained from the 3D maximum intensity projection images that were generated from VOI delineation on SPECT/CT images. A standardized density value was used to calculate the organ masses while keeping the tumour density the same as the liver density [20].

Absorbed dose estimation in systemic radionuclide therapy and intra-arterial radionuclide therapy treatment

The absorbed dose per unit administered activity (DpA) (mGy/MBq) in each organ and tumour lesion was computed using OLINDA EXM 2.0 software (Vanderbilt University, Nashville, TN, USA)[21]. The input parameters for this software are radionuclide selection, NCA and mass of each organ, which was directly obtained from the DTK software after the segmentation. The organ-absorbed dose was determined by the following formula:

$$AD = N \times DF(6)$$

Where n is the number of disintegrations in the source organ and 'df' is the dose factor which is given by:

$$Dose\ Factor\ =\ \frac{k\sum_i N_i \quad \mathrm{E}_i \quad \varphi_i\ w_r}{m}$$

where k is a constant for unit conversation (Gy-kg/MBq-s-MeV or rad-g/mCi-h-MeV), N is the number of emissions with energy E, i represents the type of emission, φ is absorbed fraction, W_r is the radiation weighting factor and m is mass of the organ.

The tumour dose estimation was performed using a unit sphere density tumour model with pre-calculated S values for ^{177}Lu and masses from 0.01 to 6000 g [22].

Statistical analysis

A statistical software called R Analytics (open-source software for statistical analysis in the public domain) was used for all statistical analyses. As a result, all parameters are expressed as mean ± SD, median, interquartile range and range. In both groups, NCA and absorbed dose per unit injected activity in organ and tumour lesions were tested for significance using a non-parametric univariate Welch's t-test (P value < 0.05). Box and whisker plot was used to see and compare the dosimetry data results between both groups of patients.

Results

Organ masses (g), organ and remainder body NCA calculated for dose estimation in the present study are mentioned in Tables 4 and 5. A statistically significant difference was noted in the remainder body NCA estimated from SRT and IART (P < 0.05) (Fig. 3). The mean absorbed DpA (mGy/MBq) to kidneys, spleen, liver and lungs in ^{177}Lu-DOTATATE SRT treatment was 0.36 ± 0.28, 0.46 ± 0.31, 0.07 ± 0.04 and 0.009 ± 0.01, respectively. Similarly mean absorbed DpA to kidneys, spleen, liver and lungs in ^{177}Lu-DOTATATE IART treatment was 0.17 ± 0.09, 0.29 ± 0.13, 0.1 ± 0.07 and

Table 4 Organ and tumour masses (g)

	SRT			IART			
	Mean ± SD	50th (25th/75th)	Range	Mean ± SD	50th (25th/75th)	Range	*P* value
Kidneys (g)	318.7 ± 51.7	313.4 (281.4/341.2)	227.8–413	305.5 ± 62.6	298.1 (236.8/367.5)	186.4–438.3	0.81
Spleen (g)	153.2 ± 71.4	149.1 (122.9/218.4)	62.7–270.9	121.9 ± 28.5	120.2 (97.07/149.1)	79.38–163.8	0.08
Liver (g)	1841 ± 950	1376.4 (1216.5/2130.5)	996.5–4354.1	1761.2 ± 748	1210.1 (1012.2/2230.1)	991.3–3861.1	0.42
Lungs (g)	2363.4 ± 684.7	2357.7 (1811.2/2625)	1281–3865	1870.7 ± 612.3	1963.5 (1349.2/2383.5)	874.6–2698.5	0.16
Tumours (g)	475.5 ± 960.9	54.4 (23.2/565.3)	6.4–3675	451.6 ± 745.7	49.1 (19.6/592.1)	7.6–3221.5	0.55

P = significance of difference of organ and tumour masses between systemic peptide receptor radionuclide therapy (systemic radionuclide therapy) and intra-arterial peptide receptor radionuclide therapy (intra-arterial radionuclide therapy).
IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.

Table 5 Normalized cumulated activity of organs, remainder body and tumours obtained by Dosimetry Toolkit

	Kidneys (h)	Spleen (h)	Liver (h)	Lungs (h)	Remainder body (h)	Tumours (h)
SRT						
Mean ± SD	1.27 ± 1.22	0.87 ± 0.62	1.41 ± 1.20	0.19 ± 0.34	54.66 ± 8.53	3.98 ± 9.35
50th (25th/75th)	0.87 (0.65/1.39)	0.69 (0.36/1.12)	0.89 (0.5/1.8)	0.07 (0.05/0.18)	56.1 (47.3/61.2)	0.25 (0.04/0.98)
Range	0.09–4.69	0.15–2.13	0.44–4.92	0.01–1.42	39.4–71	0.01–43.08
IART						
Mean ± SD	0.6 ± 0.37	0.5 ± 0.19	1.55 ± 1.10	0.11 ± 0.08	41.54 ± 6.60	8 ± 11.83
50th (25th/75th)	0.73 (0.23/0.82)	0.52 (0.35/0.65)	1.12 (0.86/1.91)	0.08 (0.06/0.13)	39 (37.4/46.5)	0.35 (0.11/13.94)
Range	0.14–1.4	0.17–0.76	0.5–4.3	0.05–0.3	33.26–55	0.01–38.46
P value	0.07	0.053	0.77	0.41	0.0002	0.23

IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.
P = significance of difference between systemic peptide receptor radionuclide therapy (systemic radionuclide therapy) and intra-arterial peptide receptor radionuclide therapy (intra-arterial radionuclide therapy) (Welch's *t*-test).

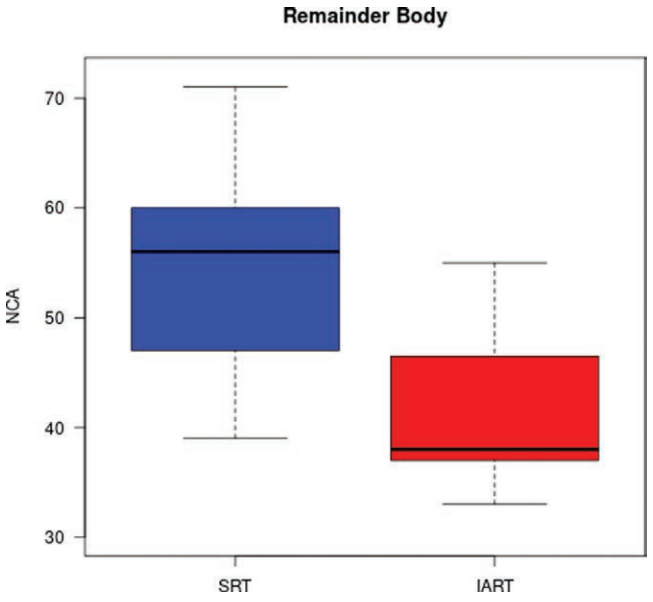
0.005 ± 0.001, respectively. The details of the absorbed doses are given in Table 6. The average post-SRT and IART imaging time points were 2.13 ± 0.29 h, 4.25 ± 0.49 h, 24.21 ± 0.65 h, 71.39 ± 1.13 h and 167.53 ± 1.73 h; 2.03 ± 0.24 h, 4.55 ± 0.38 h, 24.34 ± 0.68 h, 71.96 ± 0.9 h and 165.23 ± 1.72 h, respectively. Additionally, a SPECT/CT scan for SRT and IART was performed at 24.66 ± 0.58 h and 24.96 ± 0.52 h, respectively. A comparison of absorbed doses received by the organs from the SRT and IART treatment is presented using a box and whisker plot in Figs. 4 and 5.

Organ doses from ^{177}Lu-DOTATATE systemic radionuclide therapy and intra-arterial radionuclide therapy treatment

The detailed absorbed doses received by organs from intravenous (SRT) and intra-arterial (IART) injections of ^{177}Lu-DOTATATE are discussed here. The mean absorbed dose to kidneys, spleen, liver and lungs was 2.62 ± 2.03, 3.34 ± 2.25, 0.50 ± 0.29 and 0.06 ± 0.07 Gy, respectively in SRT treatment and 1.22 ± 0.64, 2.09 ± 6.71, 0.72 ± 0.50 and 0.03 ± 0.007 Gy, in IART treatment.

The median DpA of kidneys and spleen determined in IART treatment was compared to SRT treatment and found to be decreased by 30.7% (P = 0.03) and 37.5% (P = 0.08), where it was found to be increased by 40% (P = 0.26) and 8.1% (P = 0.28) in liver and lungs.

Fig. 3



Box plot of (a) kidneys and (b) tumour absorbed doses (DpA) obtained from SRT and IART treatment. DpA, dose per unit administered activity; IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.

Normalized cumulated activity and absorbed dose to hepatic metastatic sites from ^{177}Lu-DOTATATE systemic radionuclide therapy and intra-arterial radionuclide therapy treatment

Metastatic hepatic lesions were assessed for both SRT (n = 39) and IART treatment (n = 46). The details of NCA and DpA in tumour lesions are mentioned in Tables 5 and 6. The mean masses of the tumour for SRT and IART treatment were 475.5 ± 960.9 g and 451.6 ± 745.7 g (Table 4). The mean absorbed dose received by tumours from SRT and IART treatment with ^{177}Lu-DOTATATE was 8.08 ± 5.82 and 15.37 ± 13.64 Gy, respectively. The median DpA of tumours determined in IART treatment was compared to SRT treatment and found to be increased by 62.2% (P = 0.04). A comparison of the tumour DpA obtained from the SRT and IART treatment is presented using a box and whisker plot in Fig. 5.

IART treatment with ^{177}Lu-DOTATATE has a lower overall systemic dose compared to SRT treatment (Fig. 6).

Discussion

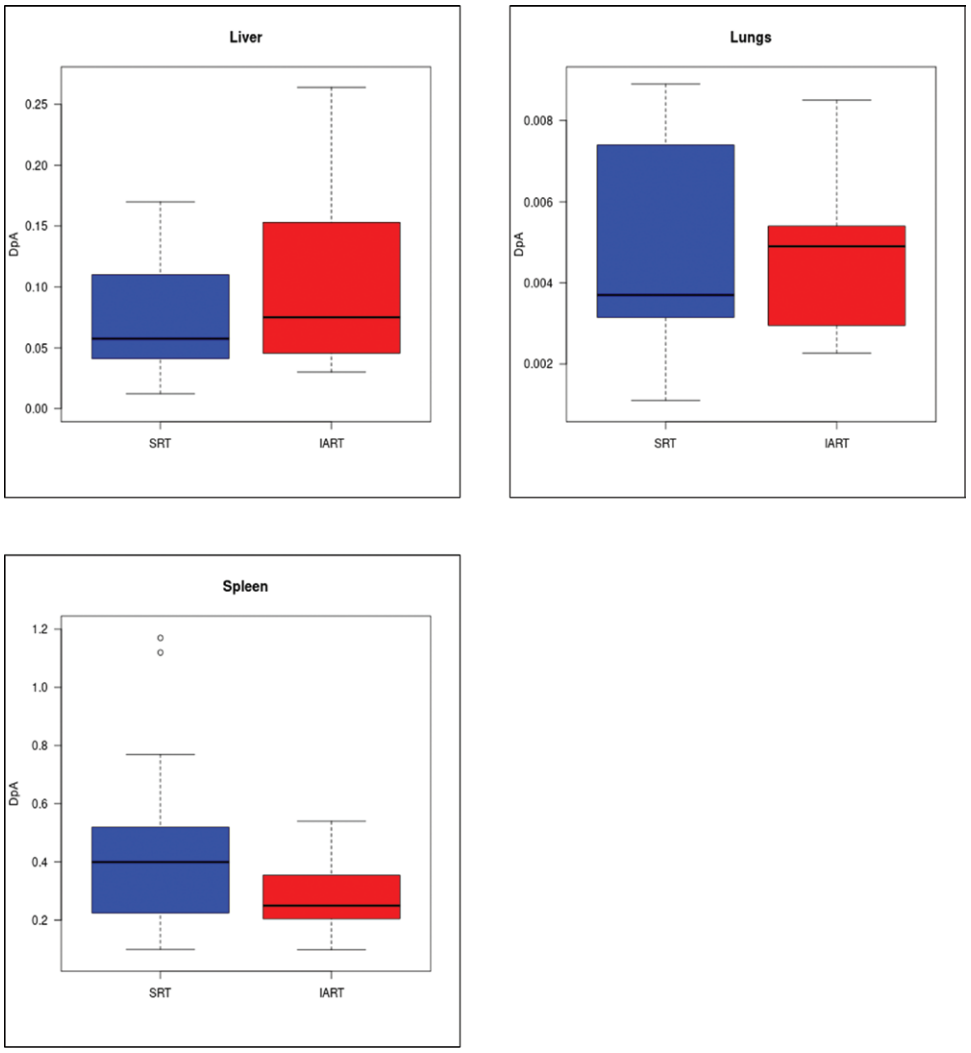
As a result of treatment with ^{177}Lu-DOTATATE SRT, the PFS and OS of many patients with metastasized GEP NETs have improved significantly; however, treatment of patients with bulky liver metastases still has a poor prognosis after the standard PRRT treatment [8]. This is mainly due to the dissipation of a certain amount of intravenously injected activity within the

Table 6 Absorbed dose per unit administered activity in the organs and tumours obtained by Dosimetry Toolkit

	Kidneys (mGy/MBq)	Spleen (mGy/MBq)	Liver (mGy/MBq)	Lungs (mGy/MBq)	Tumours (mGy/MBq)
SRT					
mean ± SD	0.36 ± 0.28	0.46 ± 0.31	0.07 ± 0.04	0.009 ± 0.01	1.11 ± 0.8
50th (25th/75th)	0.26 (0.21/0.36)	0.40 (0.21/0.53)	0.05 (0.03/0.11)	0.0037 (0.0031/0.0079)	0.9 (0.54/1.6)
Range	0.07–1.12	0.1–1.17	0.01–0.17	0.0011–0.06	0.08–3.4
IART					
mean ± SD	0.17 ± 0.09	0.29 ± 0.93	0.1 ± 0.07	0.005 ± 0.001	2.13 ± 1.89
50th (25th/75th)	0.18 (0.07/0.23)	0.25 (0.20/0.38)	0.07 (0.04/0.15)	0.004 (0.003/0.006)	1.46 (0.45/3.59)
Range	0.04–0.34	0.09–0.54	0.03–0.26	0.002–0.008	0.004–6.79
P value	0.03	0.08	0.26	0.28	0.04

IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.
P = significance of difference between systemic peptide receptor radionuclide therapy (systemic radionuclide therapy) and intra-arterial peptide receptor radionuclide therapy (intra-arterial radionuclide therapy) (Welch's t-test).

Fig. 4

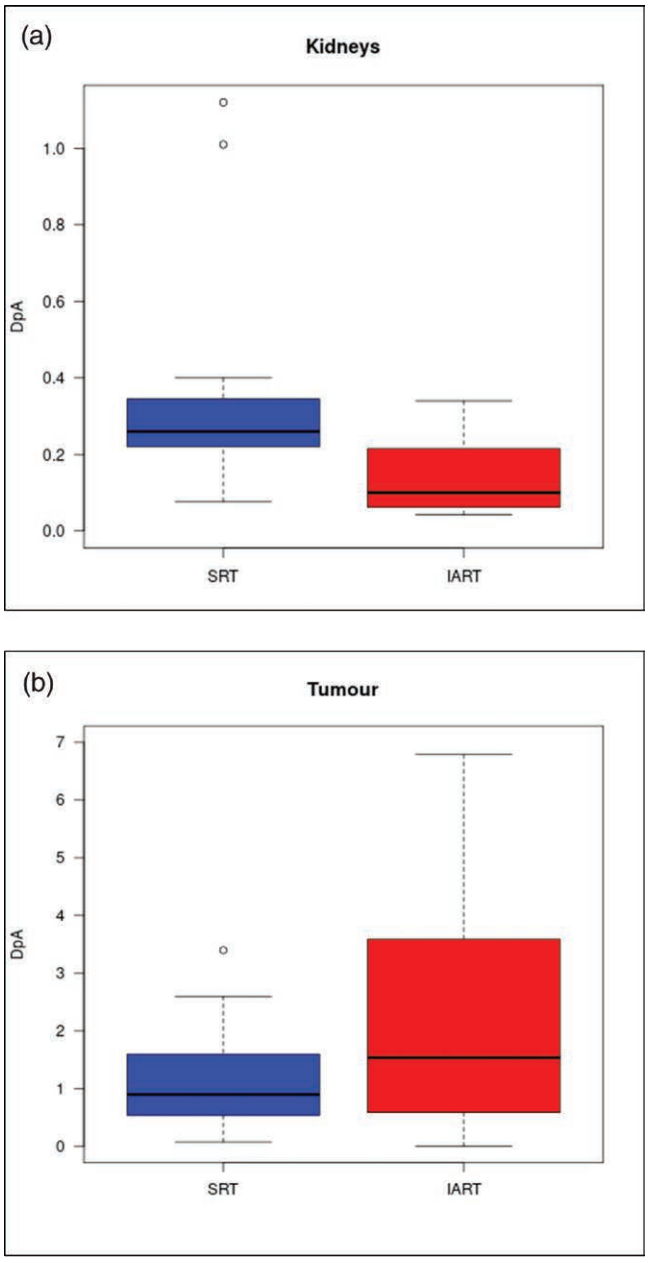


Box plot of (a) liver (b) lungs and (c) spleen absorbed doses (DpA) obtained from SRT and IART treatment. DpA, dose per unit administered activity; IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.

systemic circulation, which minimizes the concentration of ^{177}Lu-DOTATATE in overexpressed SSTR-positive intrahepatic tumours. In order to achieve a higher hepatic intratumoral concentration of ^{177}Lu-DOTATATE, intra-arterial administration may be a useful and effective strategy to enhance the overall treatment outcome. This study examined the overall effectiveness of ^{177}Lu-DOTATATE IART treatment to hepatic metastatic sites in patients with GEP NET from a dosimetry perspective.

To date, very few dosimetry studies have been conducted on intra-arterial administration. In the present study, IART treatment shows higher tumour concentration with a fold change of two as compared to SRT treatment due to the fact of the first-pass effect. A few ^{177}Lu-DOTATAE studies have also noted higher tumour concentrations in patients receiving intra-arterial treatment [13,16]. Kratochwil *et al.* found approximately 3.75 times higher standardized uptake values post intra-arterial administration of ^{68}Ga-DOTATOC [17]. Another diagnostic ^{111}In-octreotide SPECT study also demonstrates higher tumour concentration in liver metastases after intra-arterial administration as compared to intravenous administration [18]. The presence of higher levels of activity in liver metastases may result in a better response and survival rate. Previous studies have demonstrated good therapeutic efficacy and response rate with reduced side effects in patients treated with intra-arterial administration of PRRT [23,24]; however, there is a study that didn't report a significant increase in tumour concentration of PRRT in intra-arterial administration as compared to intravenous administration [25]. This is most likely due to the SSTR saturation because both ^{68}Ga-DOTATOC and ^{90}Y-DOTATOC were administered alongside.

Fig. 5



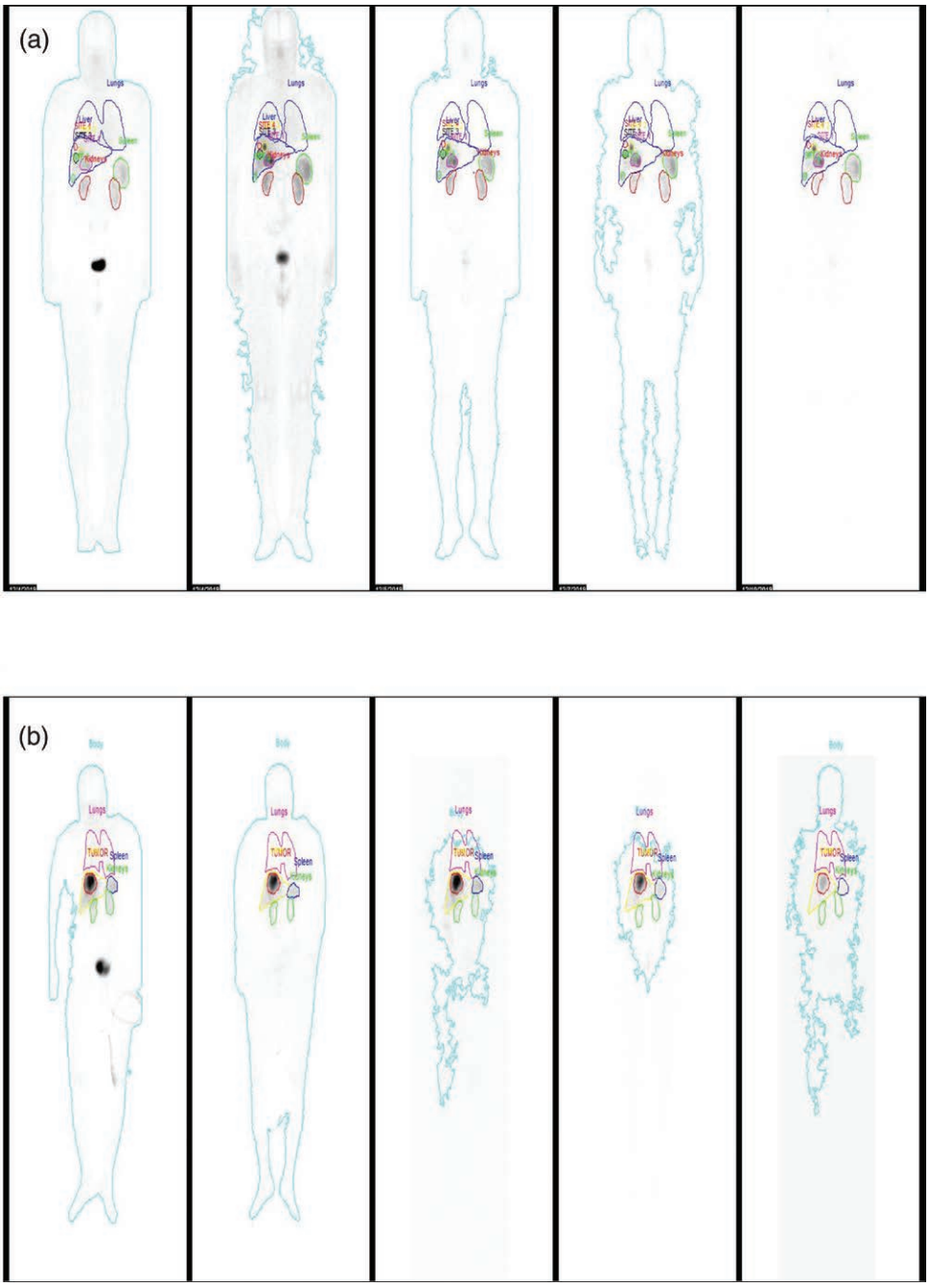
Box plot of remainder body normalized cumulated activity (NCA) obtained from SRT and IART treatment. IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.

This study found that intra-arterial administration of ^{177}Lu-DOTATATE resulted in less whole-body NCA than intravenous administration. These findings suggest that a reduction in systemic toxicity can be achieved with intra-arterial administration. This is due to the fact that some amount of radiopharmaceutical is partially trapped by hepatic tumour lesions as a result of the first pass and doesn't reach the systemic circulation thus minimizing systemic absorbed dose and associated damages. Kratochwil *et al*. observed moderate acute haematologic toxicity with no acute renal toxicity [26]. He also revealed that renal toxicity might be reduced with the intra-arterial approach. In studies, renal and systemic toxicity have been reported as the common adverse effects of intravenous PRRT [25,27]. We also demonstrated a lesser dose to normal hepatic tissues despite administering the radiopeptide directly into the hepatic artery. Therefore, the side effects of intra-arterial treatment may be less than those associated with other established treatments. In contrast to our results, Kratochwil *et al*. also found PRRT treatment less toxic post-intra-arterial administration [26]; however, Thakral *et al*. observed a higher dose in the liver with intravenous administration, which could be due to the delineation technique and threshold used to segregate normal liver tissues from metastatic liver sites [16].

The intra-arterial PRRT treatment could be a useful approach in order to increase overall treatment efficiency by increasing the number of treatment cycles or administered activities. It is a standard practice to give systemic ^{177}Lu- DOTATATE therapy in 3–5 cycles of 7.4 GBq activity, keeping the renal dose, red marrow dose and liver dose below 23 Gy, 3 Gy and 40 Gy, respectively for non-compromised patients [4,28]. Also absorbed doses are reported to be received in the range of 0.62–0.9 Gy/GBq for kidneys, 0.02–0.07 Gy/GBq for red marrow and 0.13–1.10 Gy/GBq for the liver [28]. As per the literature, the kidneys seem to be the most vulnerable organ among all the organs. In our study, the dose received by the kidneys with intra-arterial administration was in a range of 0.04–0.34 mGy/MBq. After considering the maximum tolerance limit of kidneys, the patients can be treated beyond five cycles with standard 7.4 GBq intra-arterial administration or the number of treatment cycles can be reduced further with higher administered activity. This might be of added value in the future for non-compromised patients with better response and survival.

The present study has some limitations. The number of patients included in this study is rather small (n = 48). The dosimetric comparison between SRT and IART was done between two different patient populations; however patient characteristics were comparable between both groups of patients. Further research needs to be conducted with large patient data to implement the IART technique in routine clinical practice. According to our dosimetry comparison, IART delivers high radiation doses to tumour sites with a lower systemic dose than SRT treatment, however, the clinical outcome of patients has yet to be determined if the IART approach improves them. In future studies, a combined procedure of IART with SRT can also be evaluated for extrahepatic disease.

Fig. 6



A series of post-therapeutic whole-body images obtained after (a) 177Lu-DOTATATE SRT treatment and (b) 177Lu-DOTATATE IART treatment. Treatment with IART results in higher tumour uptake and reduced systemic activity. IART, intra-arterial radionuclide therapy; SRT, systemic radionuclide therapy.

Conclusion

IART treatment with ^{177}Lu-DOTATATE significantly increases tumour dose while reducing overall systemic toxicity in comparison to SRT treatment. After considering the maximum tolerance limit of kidneys which is known as one of the most vulnerable organs of the system in PRRT, the number of treatment cycles and injected activity can be optimized further with intra-arterial administration for better response and survival in patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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