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ORIGINAL ARTICLE

Can the Standardized Uptake Values derived from Diagnostic ^{68}Ga-DOTATATE PET/CT Imaging Predict the Radiation Dose delivered to the Metastatic Liver NET Lesions on ^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy?

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ABSTRACT

Introduction: Neuroendocrine neoplasms express somatostatin receptors, enabling the use of somatostatin analogs for molecular imaging, when labeled with the positron-emitter ^{68}Ga for receptor positron emission tomography/computed tomography (PET/CT), and targeted radionuclide therapy, when labeled with beta-emitters, e.g. ^{90}Y and ^{177}Lu.

Aim: To investigate if ^{68}Ga-DOTATATE PET-derived standardized uptake values (SUV) correlate with the dose delivered to the liver lesions following ^{177}Lu-DOTATATE radionuclide therapy in patients with neuroendocrine neoplasms.

Materials and methods: Twelve adult (8M: 4F; mean age: 55.9 ± 14.5 years; range: 23-78 years) patients with documented neuroendocrine tumor (NET) disease and liver metastases were enrolled in the study. Ten patients were subjected to ^{68}Ga-DOTATATE and one patient each underwent ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTANOC diagnostic PET/CT imaging. Subsequently, on the basis of positive PET/CT scan findings for the metastatic NET disease, all these patients were subjected to peptide receptor radionuclide therapy (PRRNT) with ^{177}Lu-DOTATATE. The reconstructed PET/CT data was used to calculate the SUVs on the identifiable liver lesions. The scintigraphic data acquired (anterior and posterior whole body images) following therapeutic doses of ^{177}Lu-DOTATATE were subjected to the quantitative analysis (HERMES workstation and OLINDA/EXM software) to calculate the dose delivered to the hepatic lesions.

Results: The initial results of this preliminary study indicate poor correlation between SUV and the tumor dose and the linear regression analysis provided R2 values which explained only a small fraction of the total variance.

Conclusion: The SUVs derived from ^{68}Ga-DOTA-peptide PET/CT images should be used with caution for the prediction of tumor dose on ^{177}Lu-DOTA-peptide therapy as there are large intra- and interpatient variability. Further studies with large numbers of patients are warranted to establish such a correlation between SUV, tumor dose and the response assessment.

Keywords: ^{68}Ga-DOTATATE, Positron emission tomography/computed tomography, Neuroendocrine tumors, ^{177}Lu-DOTATATE, Peptide receptor radionuclide therapy, Standardized uptake values, Dosimetry.

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INTRODUCTION

A major factor in the evaluation of newer radiopharmaceuticals used for diagnosis and treatment is the absorbed dose from internally deposited radionuclides. Metastasized neuroendocrine tumors (NETs) have only a few treatment options. As majority of the NETs or gastroenteropancreatic (GEP) tumors possess somatostatin receptors (SSTRs) and therefore, can be diagnosed and treated with radiolabeled octreotide analogs.[1] ^{68}Ga-DOTA-[Tyr^3]octreotide (DOTA-TOC), ^{68}Ga-DOTA-[Tyr^3] octreotate (DOTATATE) or ^{68}Ga-DOTA-[1-NaI^3]octreotide (DOTANOC) have been used effectively for the accurate diagnosis of NETs due to the high affinity of these radioligands to the SSTR expression on these tumors.[2-5]

Radiopeptide therapy in patients with metastasized NETs is most commonly performed by using yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu).[6,7] ^{90}Y, being a pure β-emitter, does not allow the direct measurements of the dosimetric data, only the indirect estimates are possible with the use of ^{111}In-peptide that mimic the biodistribution and dose delivery response of ^{90}Y. On the contrary, ^{177}Lu despite having β-emission and good labeling efficiency with the octreotide analogs also have gamma emission suitable for scintigraphy and appropriate dosimetry. Therefore, ^{177}Lu-labeled DOTATOC/TATE are the most suitable radiopeptides for treating NETs.^{177}Lu-DOTATATE has been reported to be very effective in the treatment of NETs in experimental animals and subsequently since its first clinical use in humans.[8,9] Among all the commercially available SSTR analogs, DOTANOC is reported to have the highest affinity to SSTR-3 and 5 followed by SSTR-2.[4,5] However, a recent study has shown that the higher affinity of DOTANOC to SSTR-3, 4, 5 leads to a higher uptake in normal tissue and therefore results in an increase in the whole body dose as compared to ^{177}Lu-DOTATATE.[10]

It is generally considered that the patients with NET metastatic lesions having high standardized uptake values (SUV) on ^{68}Ga-DOTA-peptide positron emission tomography (PET) have good prognosis following peptide receptor radionuclide therapy (PRRNT). But, no information exits in the literature on the correlation between the SUV values, and the dose delivered to the target lesions on PRRT. Therefore, in the present study, we report our first preliminary results on the correlation between SUV (derived from ^{68}Ga-PET data) and the tumor dose delivered to the liver target lesions after the PRRT with ^{177}Lu-DOTATATE in patients with metastatic NET disease.

MATERIALS AND METHODS

Radiochemistry

^{68}Ga was eluted from ^{68}Ge/^{68}Ga generator (Eckert and Ziegler, Berlin, Germany) and radiolabeled with peptides as ready to use (intravenous) patients' preparations were prepared in house by the Radiopharmacy Division of the Zentralklinik, Bad Berka, Germany and the detailed methodology is described elsewhere.[2]

Pure salts of DOTATOC, DOTATATE and DOTANOC were procured from JPT (JPT Peptide Technologies GmbH, Volmerstrasse 5 (UTZ) 012489, Berlin, Germany) and a standard laboratory procedure for radiolabeling peptides with ^{177}Lu was followed.[11] Briefly, a solution of 500.0 µg of 2, 5 dihydroxybenzoic acid and 50.0 µg of the corresponding DOTA-peptide in 50.0 µl of 0.4 M sodium acetate buffer (pH adjusted to 5.5) was added to 1.0 GBq of ^{177}Lu (high specific activity of ≥80.0 Ci/mg, RNP > 99%, supplied by ITG Isotope technologies, Garching GmbH, Germany) contained in 30 µl of 0.05 M HCl. The contents were heated at 90°C for 30 minutes and then diluted with 0.9% saline solution followed by appropriate sterile filtration. The radiochemical purity of the labeled DOTA-peptides was always greater than 99%.

Patients

Twelve adult patients (8M:4F; mean age: 55.9 ± 14.5 years; range: 23-78 years) having documented NET with liver metastases were enrolled in the study. Intense SSTR expression on the primary tumors and metastases rendering the patients inoperable was the inclusion criteria for considering the patients for PRRNT. Ten patients were subjected to ^{68}Ga-DOTATATE and one patient each underwent ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC diagnostic positron emission tomography/computed tomography (PET/CT) imaging. Subsequently, based on positive ^{68}Ga-PET/CT scan findings for the metastatic NET disease, all these patients were subjected to PRRNT with ^{177}Lu-DOTATATE. An informed written consent was taken from all the patients who participated in the study and the study protocol was approved by the ethics committee of the institute.

Prior to PET/CT imaging and PRRNT, the patients were instructed to intake of long-acting release preparation of sandostatin for 4 to 6 weeks and subcutaneous treatment with octreotide for at least 2 days. Patients were adequately hydrated and just before the PET/CT acquisition were administered with 1.5 L of oral contrast (Gastrografin dispersion).

The scanning was performed on a dual modality PET/CT (Biograph duo, Siemens Medical Solutions, Germany) at a mean postinjection (PI) time of 72.9 ± 12.0 minutes (range: 60-95 minutes) following an intravenous injection of a mean activity of 130.0 ± 18.5 MBq (106-182 MBq) of ^{68}Ga-labeled peptide. The patients were instructed to void the bladder and lie supine on the table with the arms extending over the head. First a topogram from the skull to the upper thighs was acquired over 1,024 mm axially in 7-8 bed positions. After administration of 100 ml of contrast (given as IV infusion), contrast enhanced CT was acquired in the craniocaudal direction with a 30-second delay. CT was performed in the spiral mode using a continuous acquisition at 130 kVp, 115 mAs, 4 mm collimation, 5 mm slice width, a table feed of 8 mm per rotation at 0.8-second rotation time and 2.4 mm slice spacing. During the CT acquisition, a limited breath hold protocol was followed and after completion of the CT acquisition, the patients were automatically moved to the PET start position (rear of the gantry) and 3D PET emission scanning started in the caudocranial direction. An emission scan time of 1 to 2 minutes (normalized to the height and weight of the patient) per bed position was used with a total emission scan time of no more than 24 minutes and a total PET/CT acquisition of about 30 minutes.

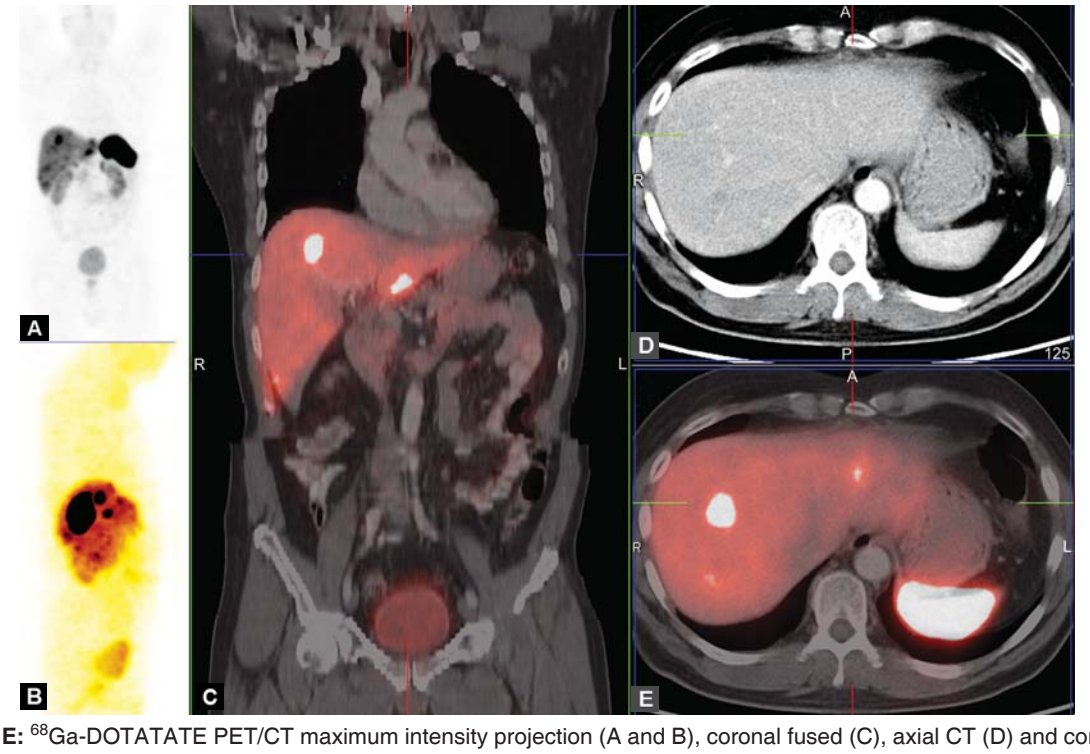
The reconstructed PET/CT images were displayed in three (cross-sectional, coronal and sagittal) different planes and all the metastatic target lesions on the liver and elsewhere were identified by two experienced nuclear medicine physicians and a radiologist. All the target lesions were subjected to a quantitative analysis to calculate the SUV_{max}, SUV_{mean} and molecular tumor volume (MTV; cm^3). In addition, the diagnostic CT data were used to calculate the thickness of liver, spleen, kidney and body thickness in the abdominal region harboring the metastatic liver disease and volumetric measurements of the target lesions.

Post PRRNT Scan

Anterior and posterior whole body images were acquired, at different time intervals following an IV infusion of ^{177}Lu-DOTATATE (mean activity: 6,711 ± 659 MBq; range: 5,500-8,500 MBq), under the dual head gamma camera (MEDISO, Medical Imaging Systems, Badapast, Hungary) peaked at 208 keV; 15% energy window, scan speed 15 cm/min) by using medium energy general purpose (MEGP) collimator. The first whole body scan acquired immediately without allowing the patients to void represented 100% of the administered radioactivity. The subsequent scans acquired at 3, 20, 44 and 68 hours following radioactivity infusion reflected only the percent fraction of the total injected activity. The quantitative analysis was carried out first on the 20 hours whole body images by drawing regions of interest (ROIs) manually over the source organ by using a dedicated HERMES computer system (Gold software version 3.0.92, HERMES, Medical Solutions, Stockholm, Sweden). The whole body anterior and posterior scans were displayed (by using the HERMES, computer algorithm, Whole Body Display whole Version 3.3) and the ROIs drawn on the 20-hour scans were applied to the scans acquired at the other four intervals. The quantification was always done by the same physicist under the guidance of a nuclear medicine physician who decided the quantifiable lesions as 'target lesions' for dosimetric evaluation. For these calculations, always the geometric mean data normalized for the background were calculated which accounted for the physical characteristics of the organ/patient and also for the counts due to the adjacent background or the underlying organs. The time-activity curves were drawn which were fitted depending upon the nature of the curve whether mono and/or biexponential function. The integration of this curve gave the total number of disintegrations or the residence times (equivalent to the cumulated activity) of the region. The effective half-lives of the radiopharmaceutical (^{177}Lu-DOTATATE) was determined by using the exponential fit-function by using a computer program (Origin Pro 7.0G). Finally, the absorbed organ and tumor doses were estimated using the residence times and the computer software OLINDA/EXM which used the S-values for the radionuclide and different phantoms. Specifically, the mean absorbed tumor doses were estimated by using the unit density sphere module of OLINDA/EXM. Dosimetry results were obtained for the whole body, normal tissue, spleen, kidneys and for liver metastatic lesions. An appropriate statistical analysis of the data was conducted to find a significant correlation, if any, between the SUV values, volumetric data of the tumors/target lesions and the dose delivered to these target lesions.

RESULTS

The patients' demographic details and the various quantitative parameters on the lesions' characterization and the dose delivered (sV) to the target lesions are presented in Table 1. A total of 27 liver metastatic lesions (range 1-6 lesions with at least 1 lesion/patient) were visualized



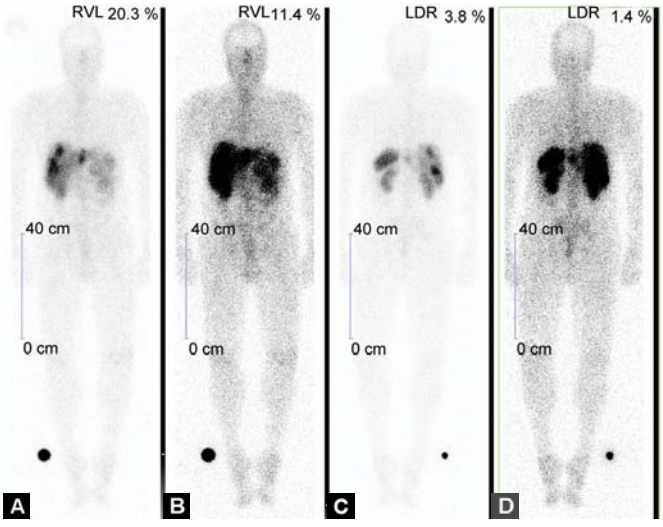
Figs 1A to E: ^{68}Ga-DOTATATE PET/CT maximum intensity projection (A and B), coronal fused (C), axial CT (D) and corresponding axial fused (E) images demonstrating multiple areas of focal tracer uptake in the liver

Table 1: Patients' demographic details, radionuclide doses, location of liver metastatic lesions and their characterization on the PET/CT imaging and the dose delivered to the target lesions on ^{177}Lu-PRRT

Sr. no.	*Age (year)*	*Sex*	*^{68}Ga-scanning PET scanning*		*Postinjection scan time (min)*	*^{177}Lu-DOTATATE-PRRT therapy dose (MBq)*	*Lesion no.*	*Location*	*Standard uptake value (SUV)*		*Mean tumor volume (cm^3)*	*Dose delivered to the tumor after ^{177}Lu-PRRT*
			Radiopharma-ceutical	Dose (MBq)					SUV_{max}	SUV_{mean}	MTV (cm^3)	sV
1.	23	M	DOTATATE	126.0	65	7000	1.	S7 (apicocentral)	7.2	5.8	5.5	8
							2.	S6 (caudal)	7.6	5.4	6.9	16
							3.	S4b (caudal)	8.5	5.3	8.0	47
2.	65	M	DOTATATE	129.0	60	7400	4.	S2-apical	10.8	6.9	12.2	111
3.	72	F	DOTATATE	122.0	65	6000	5.	S7/S8 (apicodorsal)	9.6	6.1	5.2	54
4.	54	M	DOTATATE	135.0	80	7000	6.	S2/S8	14.8	7.5	159.4	36
							7.	S4b (caudal)	11.5	7.3	63.4	81
5.	59	M	DOTATATE	182	65	7000	8.	S2 (apical)	10.1	6.6	15.3	143
6.	50	F	DOTATATE	106	65	8500	9.	S5	8.6	6.6	5.8	253
7.	45	M	DOTATATE	117.0	95	6000	10.	S6 (caudal)	17.3	8.3	5.9	80
							11.	S6 (caudal)	10.3	6.3	4.3	80
8.	66	F	DOTATOC	133.0	70	7500	12.	S8	39.4	22.6	14.4	92
							13.	S4b	37.8	22	6.6	100
							14.	S6	53.4	29.4	11.2	65
9.	62	M	DOTANOC	129.0	80	7000	15.	S3 (caudal)	16.1	8.9	22.3	83
10.	49	M	DOTATATE	117.0	70	7000	16.	S3 (caudal)	11.7	6.4	9.2	82
							17.	S4a	14.2	7.9	23.8	38
							18.	S5 (caudal central)	15.1	8.5	29.9	54
							19.	S5	13	8.1	62.2	26
11.	78	M	DOTATATE	135	65	7000	20.	S2/S3	40.6	23.8	17.2	72
							21.	S3 (caudal)	28.9	17.2	10.7	27
12.	48	F	DOTATATE	129.0	95	5500	22.	S2/S3	37.3	23	56.8	38
							23.	S5	25.1	15.2	20.9	52
							24.	S3	29.5	16	11.8	20
							25.	S6 (caudal)	37	21.7	14.5	30
							26.	S3	29.6	16.9	25.3	11
							27.	S4a	32.2	20.2	69.8	56
Mean ± SD	55.9 ± 14.5 (23-78)	8M:4F		130.0 ± 18.5 (106-182)	72.9 ± 12.0 (60-95)	6908 ± 787 (5500-8500)			21.4 ± 13.1 (7.2-53.4)	12.6 ± 7.4 (5.3-29.4)	25.9 ± 32.9 (5.2-159.4)	65 ± 49 (8-253)

Table 2: Linear regression analysis of the dose delivered to the target lesions with the SUV_{max} or SUV_{mean}

Variable	*β (SE)*	*Significance*	*Constant*	*R2*
SUV_{max}	–0.629 (0.751)	0.41	78.44	0.027
SUV_{mean}	–0.996 (1.33)	0.46	77.55	0.022



Figs 2A to D: ^{177}Lu-DOTATATE whole body dual intensity anterior (A and B) and posterior (C and D) images at 24 hours post injection

on PET/CT metabolic imaging and were quantifiable both on ^{68}Ga-DOTA-peptide PET/CT images as well on ^{177}Lu-DOTATATE therapeutic whole body scintigraphic scans. A representative ^{68}Ga-DOTATATE PET/CT scan (Figs 1A to E) showing three lesions in the right liver lobe very distinctly delineated on the transversal PET/CT fusion image. The corresponding liver lesions are also demonstrated on anterior and posterior whole body ^{177}Lu-DOTATATE images in the same patient acquired at 24 hours postinjection (Figs 2A to D).

The average SUV_{max} and SUV_{mean} for the liver metastatic lesions (n = 27) were 21.4 ± 13.1 (range: 7.2-53.4) and 12.6 ± 7.4 (range: 5.3-29.4) respectively. The mean tumor volume (MTV-cm^3 by PET/CT) was 25.9 ± 32.9 cm^3 (range: 5.2-159.4). The mean tumor dose delivered to the target liver lesions was 65.0 ± 49.0 sV (range: 8-253).

The SUV_{max} values were observed to be highly variable (7.2-53.4). For the lesion (lesion-9, patient-6, Table 1) with SUV_{max} of 8.6, the dose delivered was 253 sV. On the other hand, in the lesion (lesion-14, patient-8) with SUV_{max} of 53.4, the dose delivered was 65.0 sV.

STATISTICAL ANALYSIS

Nonparametric Spearman's test (SPPS-16 for Windows) was used to study the correlations between the various parameters. No significant correlation was observed between the SUV_{max} or SUV_{mean} with the dose delivered to the target lesions (r = 0.039 and 0.007). Linear regression analysis of dose delivered with the SUV_{max} or mean values did not reveal any significant associations (Table 2). The R2 values were very low suggesting that the equations explained only a very small fraction of the total variance.

DISCUSSION

PPRNT using the somatostatin analog [^{177}Lu-DOTA^0, Try^3] octreotide is a convincing treatment modality for metastasized NETs. The radionuclide in turn is retained in the lysosomes of the tumor cells, close to the nuclei and the irradiation to these nuclei will damage DNA leading to apoptosis and necrosis of the cell.[11] The maximal tissue range of 2 mm with ^{177}Lu appears to be more favorable for the treatment of small metastases, while ^{90}Y with a maximal range of 11.3 mm has a stronger cross fire effect and seems to have better efficiency in bigger tumors.[12,13] ^{177}Lu-labeled analogs have been reported to show less nephrotoxicity than the ^{90}Y-labeled counterparts.[14] In a recent study, Wehrmann et al[10] have reported that ^{177}Lu-DOTANOC due to its higher affinity lead to a higher uptake in normal tissue and therefore resulted in a higher whole body dose, however the uptake in tumor lesions and the mean absorbed tumor dose was higher for ^{177}Lu-DOTATATE.[10] It was thus, decided to treat our patients subsequently with ^{177}Lu-DOTATATE and to perform dosimetry to see correlation, if any, between the SUV and the dose delivered to the metastatic liver-target lesions. The currently used, regimens of cumulative dose of about 800 mCi of ^{177}Lu-DOTATATE therapy in four cycles (after 6-10 d) of 200 mCi (7,400 MBq) has been reported to be effective in treating the metastatic NET disease without any renal toxicity.[7] With this approach, approximately, 80% of the patients having progressive disease at the start of therapy are reported to attain stable disease, partial or complete remission.[12,15,16]

The uptake of the radionuclide and thus the dose delivered to the target metastatic NET lesions on PRRT with DOTATATE will largely depend upon the tissue density of SSTR-2 as the ^{177}Lu-DOTATATE used in this study exhibit high affinity to this subtype of SSTR.[4,5] Our preliminary findings indicated no significant correlation between SUV (both max and mean) and the dose delivered to the target lesion on PRRT using ^{177}Lu-DOTATATE. These findings thus, indicate that the absolute SUVs derived

on the ^{68}Ga-DOTA-peptide PET images localizing metastatic NET lesions cannot predict the dose delivered to these lesions. In other words, the PRRT response is individualized and may vary as a function of histochemical variations or SSTR expression on the different lesions. Even the two lesions in the same patient are noted to exhibit different response to PRRNT, which is observed to be independent of the SUVs derived on the ^{68}Ga-somatostatin receptor imaging. Wehrmann et al[10] have reported that although the mean absorbed tumor dose was higher for DOTATATE, but the high intra- and interpatient variability of the dosimetry results with ^{177}Lu DOTATATE and ^{177}Lu DOTANOC makes it obligatory to perform the individual patient dosimetry.

The mechanism of localization of the NETs either by ^{68}Ga-DOTATATE or ^{177}Lu-DOTATATE remains the same as the same peptide-ligand has been used both for diagnosis and PRRT in these patients. However, the variations in the affinity profiles (IC50) of somatostatin receptor subtypes for different somatostatin analogs used in different diagnostic imaging with PET/CT or SPECT/CT have been reported.[1,4,5,17,18] These results for affinity profiles for different somatostatin analogs have been summarized by Prasad et al,[3] e.g. the IC50 of ^{90}Y-DOTA-TOC and ^{68}Ga-DOTATOC for SSTR-2 are 11.0 and 2.5 respectively. The lower value represents higher receptor affinity and thus the affinity of the therapeutic ^{90}Y-DOTATOC is about four times lesser as compared to the diagnostic Ga-DOTATOC. Similarly, the affinities of ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE may also differ which can contribute toward the observed noncorrelation between the SUVs and the amount of the dose delivered to the target lesions. Also, the variations in the SSTR expression at the time of ^{68}Ga-PET imaging and ^{177}Lu therapy could be another factor which explains the absence of any correlation between the SUVs and the dose delivered to the metastatic liver lesions on PRRT.

In a recent experimental study, Meils et al[19] reported that a high SSTR-2 density on the tumor cells at every PRRNT cycle is a crucial prerequisite to enable targeting of the tumor and subsequently for the internalization of the radiolabeled somatostatin analogs. These authors reported a very strong correlation between the increased SSTR expression following low dose ^{177}Lu-DOTATATE therapy and the effectiveness of the subsequent high dose PRRNT in CA-20948 tumor-bearing rats.[19] As indicated in this experimental study, thus there is a possibility of induction of near uniform receptor expression/density by upregulation of SSTR-2 on the NET lesions/tumors by subjecting these patients to first low dose ^{177}Lu-DOTATATE radionuclide therapy. However, more detailed experimental validation of this concept is needed to establish a correlation between the SSTR expression, SUVs, dose delivered to the tumors to predict the overall response of PRRNT in metastatic NETs. The future possibility of upregulation or induction of SSTR expression to achieve significant density of these receptors on the tumor surface and subsequent treatment with high dose ^{177}Lu-DOTATATE may present a positive correlation between SUVs and the dose delivered to the tumor to predict an overall response to PRRT.

In a recent study, Ezziddin et al[20] have shown that somatostatin receptor PET imaging may predict tumor absorbed doses on PRRNT. However, our initial results indicate poor correlation between SUV and the tumor dose and the linear regression analysis provided R2 values which explained only a small fraction of the total variance. Therefore, with the currently used fractionation and cumulative PRRNT treatment protocol, the SUV derived from ^{68}Ga-DOTA-peptide PET images should be used with caution for the prediction of tumor dose on ^{177}Lu-DOTA-peptide therapy as there are large intra- and interpatient variability. However, further studies with large numbers of patients are warranted to validate the results.

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