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Tumor-to-blood ratio for assessment of somatostatin receptor density in neuroendocrine tumors using ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE

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ABSTRACT

PET/CT with ^{68}Ga-DOTA-somatostatin analogs has been tested for therapy monitoring in patients with neuroendocrine tumors (NETs). However, standardized uptake values (SUV) in tumors do not correlate with the net influx rate (K_i), as a representation of the somatostatin receptor (SSTR) expression. In this study, tumor-to-blood-ratio (TBR) was evaluated as an alternative tool for semi-quantitative assessment of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE tumor uptake and as a therapy monitoring tool for patients with NETs.

Methods

Twenty-two NET patients underwent a 45-min dynamic PET/CT scan after injection of ^{68}Ga-DOTATOC and/or ^{68}Ga-DOTATATE. K_i was determined using the Patlak method and TBR was calculated for the 40-45 min time interval.

Results

A linear relation was found between K_i and TBR, with a square of Pearson correlation (R^2) of 0.98 and 0.93 for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE, respectively.

Conclusion

High correlation was found between K_i and TBR. Hence, TBR reflects SSTR density more accurately than SUV and is suggested as the preferred metrics for semi-quantitative assessment of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE tumor uptake.

INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasms that arise from endocrine cells distributed throughout the body and have diverse biological and clinical characteristics (*1*). The feature of high cellular expression of somatostatin receptors (SSTR) in NETs enables the use of unlabeled and radiolabeled somatostatin analogs for imaging and therapy. During the past decade, positron emission tomography (PET) using gallium-68 (^{68}Ga)-labelled somatostatin analogs, such as ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE, has gradually replaced SSTR scintigraphy with ^{111}In-DTPA-octreotide (OctreoScan®) (*2, 3*) and become the standard method for SSTR imaging of NETs (*4*).

PET/CT with ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE has also been suggested as a tool for evaluation of therapy response in patients with NETs (*5-8*). For metabolic tracers such as ^{18}F-FDG, it can be assumed that the tracer's distribution volume is the whole body since glucose is consumed by all tissues, which means that the standardized uptake value (SUV) can be used as a reasonable measure of metabolism. A challenge with PET/CT using receptor ligands, such as ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, is that the distribution volume instead is confined to those tissues that in fact are taking up the tracer, which may affect the SUV quantification. In one study (*5*) it was found that the changes in tumor SUV between baseline and follow-up ^{68}Ga-DOTATOC-PET/CT did not correlate to the therapy outcome of peptide receptor radionuclide therapy. The same finding was also reported in another study (*6*), although changes in the tumor-to-spleen SUV ratio between baseline and follow-up ^{68}Ga-DOTATOC were shown more accurate than those of the tumor SUV_{max} to evaluate the response to peptide receptor radionuclide therapy. The difficulties of applying static tumor uptake measurements in these two therapy monitoring studies may, at least, partly be explained by the results in a study (*7*) on tracer kinetics of ^{68}Ga-DOTATOC and

^{68}Ga-DOTATATE. In that work, net uptake rate values (K_i), assumed to more accurately reflect SSTR density than SUV, were estimated based on dynamic PET imaging and it was found that SUV saturated (SUV >20-25) at a static value for high K_i values (K_i >0.2). Hence, SUV does not appear to reflect SSTR density for tumors with high SSTR expression. The hypothesis of the present work is that saturation in SUV for high K_i values may be explained by low availability of ^{68}Ga-DOTATOC/^{68}Ga-DOTATATE in the blood at some time after administration due to the substantial amounts of SSTR in these patients. Hence, the tumor-to-blood ratio (TBR) may be a better metrics than SUV to quantify the changes in SSTR-expression to assess NET therapy response. The aim of this study was to evaluate the correlation between K_i and TBR for patients undergoing PET/CT with ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE.

MATERIALS AND METHODS

Patients

The data in this work were collected from three different studies which all were approved by the Regional Ethics Review Board in Uppsala. All patients signed a written informed consent prior to inclusion in each study.

Twenty-two patients (11 men/11 women) mean 63 (range 47-75) years diagnosed with disseminated NETs (10 small-intestinal, 6 pancreatic, 2 rectal, 1 duodenal, 1 lung and 2 pancreatic neuroendocrine cancers), 4 grade 1 (Ki-67 <2%), 16 grade 2 (Ki-67 2-20%) and 2 grade 3 (Ki-67 =30%), confirmed by histopathology, were included. The clinical patient data are presented in Table 1. Some patients were examined with both ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE on consecutive days (N=6) while the remainder were only examined with either ^{68}Ga-DOTATATE or

^{68}Ga-DOTATOC. Sixteen patients underwent a ^{68}Ga-DOTATOC PET/CT examination after a bolus injection of 131 ± 47 MBq, 25 ± 8 μg (range, 62-198 MBq, 15-47 μg) and 13 patients underwent a ^{68}Ga-DOTATATE PET/CT examination after a bolus injection of 107 ± 31 MBq, 23 ± 9 μg (range, 76-197 MBq, 8-39 μg).

Image Acquisition and Reconstruction

The patients were examined on a Discovery ST, Discovery IQ or Discovery MI PET/CT scanner (GE Healthcare, Waukesha). They underwent a low-dose CT scan (140 kV, auto mA 20-80 mA) followed by a 45-min dynamic PET examination of the abdomen. The dynamic PET examination started simultaneously with the intravenous injection of ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE and consisted of 22 time-frames of increasing time durations (6x10, 3 x20, 3x60, 5x180, 5x300 s). All appropriate corrections were applied to the PET-data and reconstruction settings are specified in Table 2.

Image-derived Input Functions

The total radioactivity concentration in the arterial plasma was used as the input function. Volume of interest (VOI) were drawn using a 70% isocontour over the descending thoracic aorta in 10 consecutive images planes in the time frame in which the first passage of the bolus was best visualized (frame 1-10) and then projected onto all time frames in the dynamic examination generating an arterial time-activity concentration curve (NEDPAS software, VU University Medical Centre, Amsterdam (*9*)). The image-derived input functions were calculated by multiplying the arterial time-activity concentration curve with a fixed plasma to whole blood ratio

of 1.6 based on previous work (*7*), data not published (mean 1.6 for both tracers; range: 1.45 – 1.73). Blood SUV at 40-45 min was determined using the isocontour VOI (70%) in the descending aorta at the last frame of the dynamic scan.

Kinetic Analysis

Tumors with diameter >1 cm and with high tracer uptake (determined visually) were included for evaluation. Isocontour tumor VOIs (50%) were drawn in the 20-45 min (frame 18-22) summation image of the dynamic examination and were projected onto all time frames to generate tumor time-activity concentration curves. K_i was determined using the Patlak method (*10*) as previously described (*11*). SUV and TBR were computed for the last frame of the dynamic scan (i.e. 40-45 min p.i).

Statistical Analysis

The difference in SUV in blood between high (K_i>0.2) and low (K_i<0.2) K_i values was determined using a Mann-Whitney test with significant difference set to $P < 0.05$ (GraphPad Software, Inc, Prism Version 6.07, San Diego, California). In this test, one tumor per patient was included based on tumors that had the highest K_i value. Only one tumor was selected per patient since some patients had several tumors while others only had one, and inclusion of all the tumors would lead to bias of the results towards the patients with more tumours.

The relation between K_i and TBR was evaluated using linear regression and Pearson correlation and compared to the relation between K_i and SUV. In this test, all tumors were included.

A comparison of K_i, SUV_{tumor} and TBR between ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE was also performed using a Deming regression, Pearson correlation and Wilcoxon matched-pairs test (significant difference set to $P < 0.05$).

RESULTS

A total of 71 tumors was included in the study, 38 tumors in patients injected with ^{68}Ga-DOTATOC (six patients had one tumor, three had two tumors, three had three tumors, three had four tumors and one had five tumors) and 33 tumors in patients injected with ^{68}Ga-DOTATATE (four patients had one tumor, four had two tumors, two had three tumors, one had four tumors, one had five tumors and one had six tumors). As shown in Fig. 1A, SUV in aortal blood at 45 min p.i. in patients with high K_i values was significantly lower than in those with low K_i values, for ^{68}Ga-DOTATOC ($P = 0.017$, Mann-Whitney test). The difference was smaller for ^{68}Ga-DOTATATE (Fig. 1B, $P = 0.127$, Mann-Whitney test). The relation between SUV in blood and K_i is presented in Figs. 1C and 1D for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE, respectively.

A linear relation was found between K_i and TBR (all tumors included) with a Pearson correlation (R^2) of 0.98 and 0.93 for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE (Fig. 2), respectively. Comparison between K_i and SUV in tumors was performed for the same tumors and the relation is illustrated in Figs. 2C and 2D. The square of Pearson correlation between K_i and SUV in tumors using a hyperbolic fit was 0.81 and 0.78 for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE, respectively. Tumor SUV, blood SUV, TBR and K_i for each patient are also presented in Supplemental Tables 1 and 2 for both tracers.

A significant difference was found in TBR between ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE (P = 0.019, Wilcoxon matched–pairs test). However, for SUV_{tumor} and K_i there were no significant differences (SUV_{tumor}: P = 0.413 and TBR: P = 0.083, Wilcoxon matched–pairs test). A linear relation between K_i, SUV_{tumor} and TBR for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE was found with a square of Pearson correlation of 0.81, 0.76 and 0.88, respectively (Fig. 3). The slopes of the Deming regression line were 1.2, 1.1 and 1.4 for K_i, SUV_{tumor} and TBR, respectively.

DISCUSSION

Early prediction of treatment response is essential to guide tumor therapy and avoid unnecessary side effects and costs from ineffective treatments. SUV has been proposed as a measure of SSTR density in NETs but changes of the tumor SUV in ^{68}Ga-DOTATOC-PET/CT during peptide receptor radionuclide therapy have not been found to reliably correlate with the treatment outcome (*5, 6, 8*). Net uptake rate (K_i) is likely to reflect the tumor SSTR density more adequately than SUV. In a previous study (*7*) comparing ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE, it was shown that K_i and SUV did not correlated linearly for NETs, especially at high SUV values (>20-25). The present work uses partly data from the same subjects, and as seen in Figs. 2 C and 2D, the addition of more subjects did not alter this conclusion.

This present study suggests that the non-linear relation between K_i and SUV for high K_i values can be attributed to faster blood clearance in patients with a high tumor receptor expression. It was found that the SUV in blood at 45 min p.i. in patients with high K_i values were significantly lower than in those with low K_i-values for ^{68}Ga-DOTATOC (Fig. 1A). For ^{68}Ga-DOTATATE, this difference was not significant (Fig. 1B). The low blood SUV in patients with high K_i values may be overestimated because of spill-in from surrounding tissues and a positive bias in low-activity areas as commonly seen in PET, whereas the high blood SUV may be underestimated because of

partial volume effect. Taking this into consideration, the difference in blood SUV between the two groups would increase even further.

It is clearly illustrated in Figs. 2A and 2B that, contrary to the non-linear relation between K_i and SUV, there is a linear relation between K_i and TBR and that the non-linear correlation between Ki and SUV can be attributed to low availability of tracer in blood. Since plasma concentrations during the scan course of are implicitly considered when estimating K_i, differences in plasma concentration of the tracer do not affect the accuracy in determination of K_i. However, since the low blood activity concentrations will limit the absolute amount of tracer available for uptake in tissue, SUV will be affected by low plasma concentrations and will not always follow K_i. Most probably, the total amount of SSTR in some patients is so large that nearly all peptide is cleared from the plasma during the initial part of the examination time, leading to the apparent saturation of tumor SUV values. It should also be noted that the clearance rate for the individual patient is also depended on e.g. kidney function, uptake in kidneys and spleen. However, the amount of tracer in blood is probably one of the most important factors and moreover, the amount of tracer in blood is a factor that may be influenced by how much peptide that is administered whereas the SSTR expression in each tumor and their combined total SSTR expression and the patient's renal function cannot be affected.

The activity concentrations in blood were determined by delineating the aorta using a 70 % isocontour VOI. In this case, the underestimation of the activity concentration in the aorta is theoretically 6 -7 % when assuming an aorta diameter of 2.5 cm and a spatial resolution of 5 mm. The results in this paper were not corrected for this. However, since this underestimation will affect K_i and TBR equally this would not change the conclusions of the study.

The patients in this study were included from three different NET studies and thus underwent examinations on different scanners with varied reconstruction settings. As known, reconstruction

parameters affect the SUV and K_i value (*12*). However, since the reconstruction will affect K_i and SUV similarly, the variations in reconstruction settings between the scanners will not affect the conclusions of the present work. For example, the partial volume effect will similarly affect SUV and K_i and the results will consequently be the same whether the reconstruction includes correction for partial volume effect or not.

CONCLUSION

A linear relation with a high correlation was found between K_i and TBR both for ^{68}Ga-DOTATOC and ^{68}Ga DOTATATE. Hence, TBR reflects SSTR density better than SUV and would be the preferred measurement tool for semi-quantitative assessment of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE tumor uptake and as a means for NET therapy monitoring.

DISCLOSURE

No financial disclosures or conflicts of interest.

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KEY POINTS

Question

The purpose of this study was to evaluate the use of TBR as an alternative tool for semi-quantitative assessment of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE tumor uptake and as a therapy monitoring tool for patients with neuroendocrine by evaluating the relation between K_i and TBR for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE.

Pertinent Findings

Both for ^{68}Ga-DOTATOC and ^{68}Ga DOTATATE a linear relation with a high correlation was found between K_i and TBR. Hence, TBR can be used as a tool for semi-quantitative assessment of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE tumor uptake and as a means for neuroendocrine tumor therapy monitoring.

Implications for Patient Care

The finding offers a new tool for assessing tumors uptake of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE and a new therapy monitoring tool for patients with neuroendocrine tumors.

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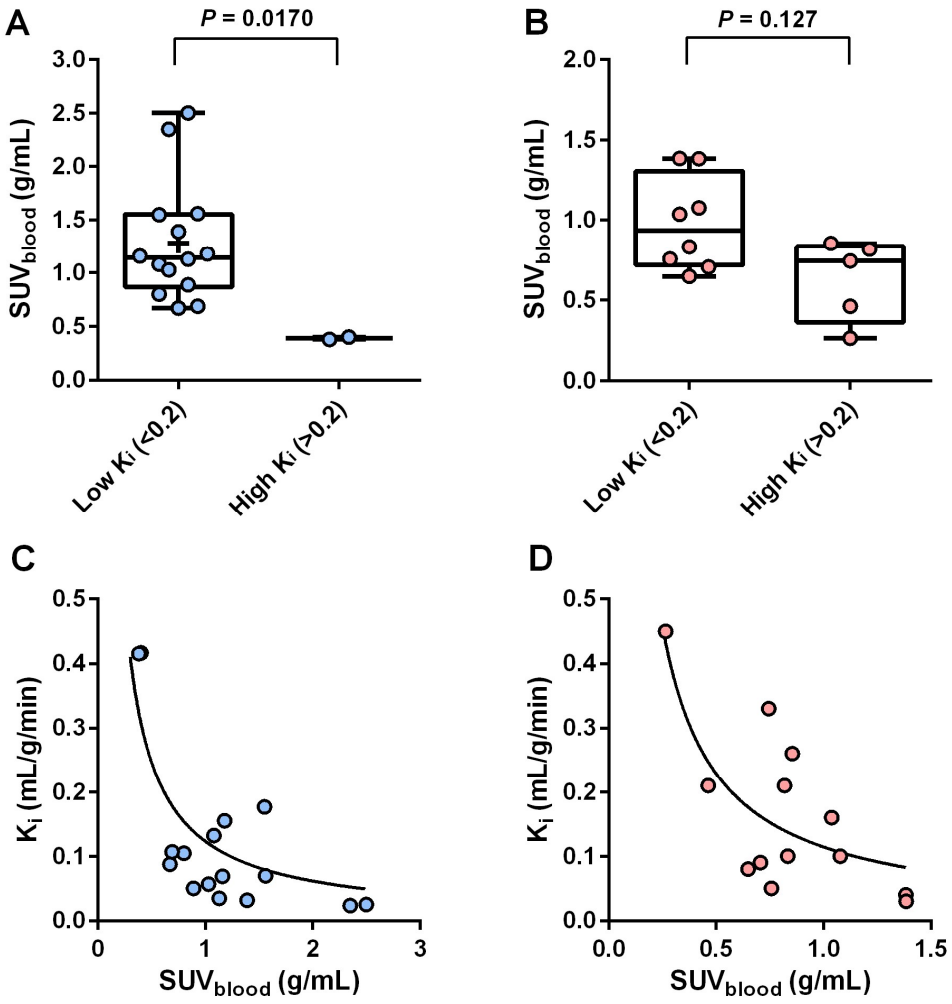

Figure 1: Boxplot of standard uptake value in blood (SUV_{blood}) at 40-45 min p.i. for ^{68}Ga-DOTATOC (A) and ^{68}Ga-DOTATATE (B) for high- and low K_i values. One tumor per patient is included in the plot. Boxes are median and interquartile range and whiskers are full range of data. Significant difference ($P < 0.05$) were found in SUV_{blood} between high and low K_i both for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE. Relation between SUV in blood and K_i for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE is presented in Figs. C and D for ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE, respectively. The solid line represents an exponential fit (Y=a/x) for visual illustration.

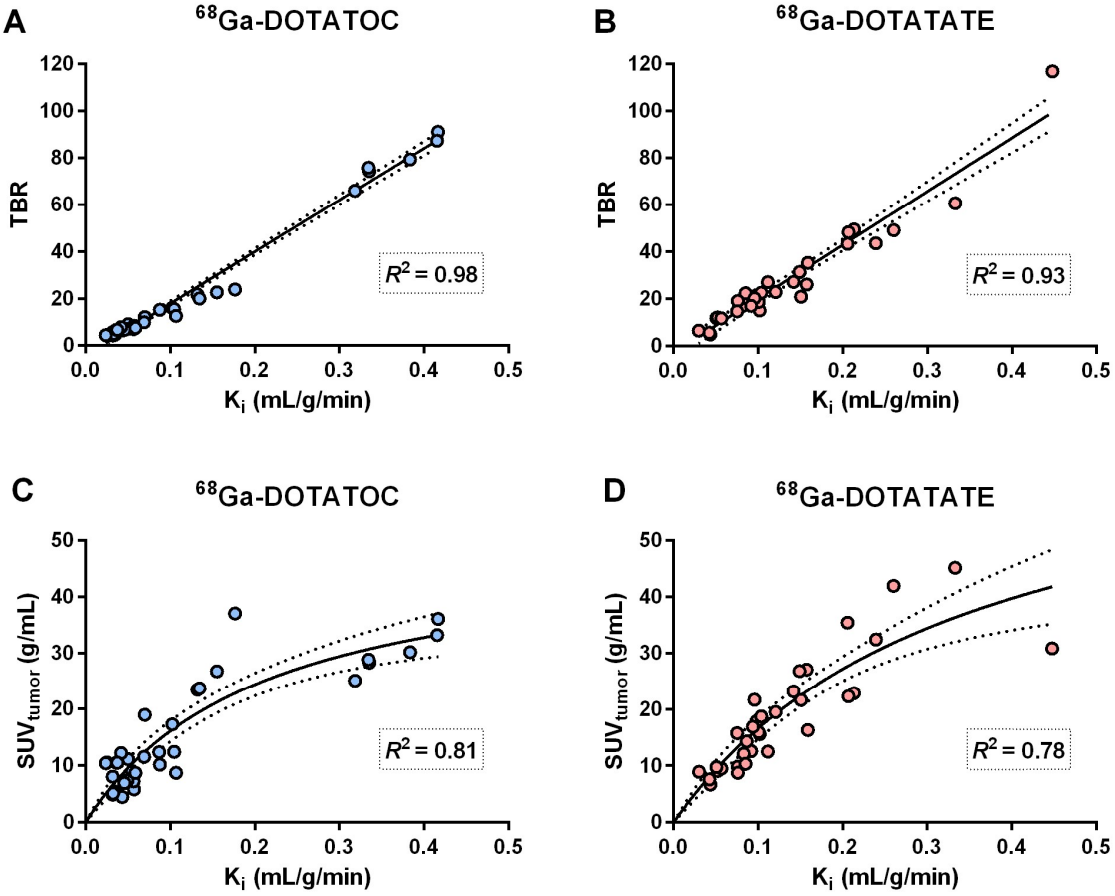

Figure 2: Correlation between K_i and tumor-to-blood-ratio (TBR) for ^{68}Ga-DOTATOC (A) and ^{68}Ga-DOTATATE (B), and between K_i and SUV in tumors for ^{68}Ga-DOTATOC (C) and ^{68}Ga-DOTATATE (D). The solid lines represent linear regression fits (A and B) and fits to a hyperbolic line (C and D), and the dashed lines the 95% confidence band of these fits.

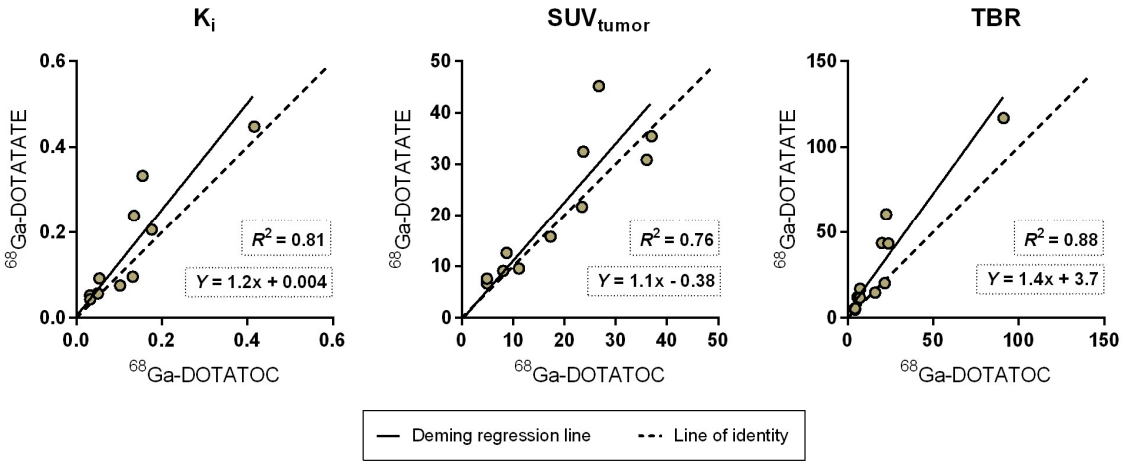

Figure 3: Comparison of K_i, SUV_{tumor} and TBR between ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE. The solid line represents a Deming regression line and the dashed line the line of identity. A significant difference was found between ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE for TBR (P = 0.019, Wilcoxon matched–pairs test), but not for K_i and SUV_{tumor} (P = 0.413 and 0.083, respectively).

Table 1: Demographics and clinical characteristics of the study patients

Gender, age	NET type (comment)	Tracer	Peptide amount (µg)	Ki-67 index	Previous surgery	History & Previous therapy	Metastases	Ongoing therapy
F, 67y	pNET/NEC (Glucagonoma)	TOC/TATE	23/23	3%	-	SSA, Streptozotocine-5FU, PRRT, transformation to NEC and carboplatine-etopside	Liver	
F, 63y	SI-NET	TOC/TATE	17/29	1%	Primary tumour	Liver trpl 1999 because of cyst disease	Liver, Mesenteric lgl	-
M, 67y	SI-NET	TOC/TATE	18/30	1%	Primary tumour	-	Liver, Mesenteric lgl	SSA
M, 50y	SI-NET	TOC/TATE	20/33	18%	Primary tumour mesenteric lgll	-	Liver, Mesenteric lgl, Retroperitoneal lgll	SSA
M, 64y	pNEC	TOC/TATE	26/25	30%	-	Avastin, Temozolamide	Liver	-
F, 73y	pNET	TOC/TATE	22/22	3%	-	Streptozotocine-5FU	Liver, Abdominal lgll	SSA
M, 57y	SI-NET	TOC	25	3 %	-	SSA	Abdominal lgll, mesenteric lgl	SSA
M, 53y	pNET (Malignant insulinoma)	TOC	18	3%	Primary tumour	Streptozotocine-5FU, Sirtex	Liver, Mesenteric lgl	Afinitor
F, 72y	pNET (MEN-1, Gastrin producing)	TOC	15	No biopsy	-	-	Retroperitoneal lgll	-
M, 51y	pNET	TOC	22	3%	Primary tumour	-	Retroperitoneal lgll	-
M, 74y	SI-NET	TOC	23	1%	-	-	Mestenteric lgll	-
F, 67y	pNET	TOC	25	2%	-	Streptozotocine-5FU	Liver	-
M, 50y	SI-NET	TOC	47	4%	-	-	Liver, mesenteric lgl, peritoneal carcinomatosis	SSA
F, 52y*	SI-NET	TOC	25	5%	-	-	Liver, mesenteric-thoracic-neck lgll, bone, breast, ovary	SSA
F, 69y	SI-NET	TOC	27	9%	-	-	Liver, bone	SSA
F, 47y	SI-NET	TOC	41	9%	-	-	Liver, mestenteric lgl, abdominal and retroperitoneal lgll	SSA
M, 72y	Rectal NET	TATE	13	30%	-	-	Liver, pararectal lgll	-
F, 69y	SI-NET	TATE	22	12%	-	-	Liver, peritoneal carcinomatosis	SSA
M, 67y	pNET	TATE	8	17%	-	-	Liver, abdominal lgll, bone	SSA
M, 75y	Rectal NET	TATE	14	10%	-	-	Liver, abdominal lgll, peritoneal carcinomatosis	-
F, 53y*	SI-NET	TATE	16	5%	Primary tumour	-	Liver, Abdominal lgll, bone, breast, lung	SSA
F, 58y	Duodenal-NET (Gastrinoma)	TATE	22	3 %	Primary tumour liver resection, RF	-	Liver	SSA
F, 75y	Atypical lung-NET	TATE	39	6 %				SSA

F = Female, M = Male, * = Same patient, TOC = ^{68}Ga-DOTATOC, TATE = ^{68}Ga-DOTATATE, SSA = long acting somatostatin analogue, PRRT = peptide receptor radiotherapy, trpl = transplantation, Sirtex = trans-arterial liver embolization with ^{90}Y-spheres, lgl =single lymph node, lgll = multiple lymph nodes, NET = neuroendocrine tumor, NEC = neuroendocrine carcinoma

Table 2: Reconstruction settings for the three different scanners.

Reconstruction settings	**Discovery ST**	**Discovery IQ**	**Discovery MI**
Reconstruction algorithm	OSEM	OSEM with PSF modeling	ToF-OSEM with PSF modeling
Iterations/subsets	2/28	4/12	3/16
Post filter (mm)	5	4	5
Matrix size	128x128	256x256	256x256
Pixel size (mm)	3.91x3.91x3.27	1.95x1.95x3.26	1.95x1.95x2.79

Supplemental Table 1: Standard uptake value in tumor (SUV_{tumor}), standard uptake value in blood (SUV_{blood}), tumor-to-blood ratio (TBR) and net influx rate (K_i) in patients injected with ^{68}Ga-DOTATOC.

Patient	Tumor	SUV_{tumor} (g/mL)	SUV_{blood} (g/mL)	TBR	K_i (mL/g/min)
TOC 1	1	23.43	1.08	21.70	0.132
	2	17.33	1.08	16.05	0.103
TOC 2	3	8.05	1.39	5.79	0.032
TOC 3	4	23.69	1.18	20.04	0.135
	5	8.71	1.18	7.37	0.054
	6	26.74	1.18	22.61	0.155
TOC 4	7	5.38	1.13	4.76	0.035
	8	4.88	1.13	4.31	0.032
	9	4.91	1.13	4.34	0.032
TOC 5	10	36.06	0.40	91.19	0.417
TOC 6	11	10.56	2.50	4.22	0.025
TOC 7	12	37.02	1.55	23.85	0.177
	13	11.13	1.55	7.17	0.050
TOC 8	14	10.21	0.67	15.25	0.088
TOC 9	15	8.12	0.89	9.13	0.050
TOC 10	16	12.44	0.80	15.55	0.105
	17	12.43	0.80	15.54	0.087
TOC 11	18	4.46	0.69	6.48	0.043
	19	5.83	0.69	8.46	0.057
	20	8.76	0.69	12.69	0.107
TOC 12	21	28.27	0.38	74.38	0.335
	22	33.20	0.38	87.36	0.415
	23	30.16	0.38	79.38	0.384
	24	25.05	0.38	65.91	0.319
	25	28.82	0.38	75.85	0.334
TOC 13	26	7.25	1.03	7.04	0.057
	27	5.11	1.03	4.96	0.032
	28	7.36	1.03	7.15	0.049
	29	6.95	1.03	6.74	0.046
TOC 14	30	12.25	1.56	7.85	0.042
	31	10.55	1.56	6.76	0.036
	32	19.01	1.56	12.19	0.070
	33	10.54	1.56	6.76	0.037
TOC 15	34	10.42	2.35	4.44	0.024
TOC 16	35	11.50	1.16	9.92	0.069
	36	8.15	1.16	7.02	0.050
	37	8.97	1.16	7.74	0.055
	38	8.71	1.16	7.51	0.059

Supplemental Table 2: Standard uptake value in tumor (SUV_{tumor}), standard uptake value in blood (SUV_{blood}), tumor-to-blood ratio (TBR) and net influx rate (K_i) in patients injected with ^{68}Ga-DOTATATE.

Patient	Tumor	SUV_{tumor} (g/mL)	SUV_{blood} (g/mL)	TBR	K_i (mL/g/min)
TATE 1	1	9.83	0.65	15.18	0.076
TATE 2	2	15.62	1.04	15.05	0.102
	3	27.05	1.04	26.06	0.158
	4	21.65	1.04	20.85	0.151
TATE 3	5	19.51	0.85	22.84	0.121
	6	42.00	0.85	49.15	0.260
	7	26.80	0.85	31.37	0.149
	8	23.19	0.85	27.14	0.142
	9	15.93	0.85	18.65	0.101
TATE 4	10	12.14	0.71	17.18	0.083
	11	14.31	0.71	20.26	0.086
TATE 5	12	9.76	0.83	11.72	0.051
	13	17.89	0.83	21.48	0.098
	14	18.73	0.83	22.50	0.104
	15	16.88	0.83	20.27	0.094
TATE 6	16	22.86	0.46	49.48	0.213
	17	12.51	0.46	27.08	0.112
	18	22.31	0.46	48.29	0.207
	19	16.30	0.46	35.29	0.159
	20	10.34	0.46	22.39	0.085
	21	8.77	0.46	19.00	0.076
TATE 7	22	21.69	1.08	20.14	0.096
	23	15.78	1.08	14.65	0.075
TATE 8	24	9.11	0.76	12.03	0.052
TATE 9	25	12.61	0.74	16.92	0.092
	26	32.44	0.74	43.56	0.239
	27	45.18	0.74	60.65	0.333
TATE 10	28	6.70	1.38	4.84	0.043
	29	7.62	1.38	5.51	0.042
TATE 11	30	30.87	0.26	116.94	0.448
TATE 12	31	8.92	1.38	6.44	0.030
	32	35.45	0.82	43.31	0.206
	33	9.54	0.82	11.66	0.057