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ORIGINAL ARTICLE

Influence of lanreotide on uptake of ^{68}Ga-DOTATATE in patients with neuroendocrine tumours: a prospective intra-patient evaluation

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Abstract

Introduction Somatostatin receptor imaging with PET is the standard of care for patients with a neuroendocrine tumour (NET). Since therapy and imaging with somatostatin analogues utilize the same receptor, current guidelines recommend withdrawing long-acting somatostatin analogues for 3-4 weeks prior to somatostatin receptor PET imaging. The aim of this study is to prospectively assess the effect of lanreotide use on the uptake of ^{68}Ga-DOTATATE intra-individually 1 day prior to and 1 day post injection of lanreotide.

Methods Thirty-four patients with metastatic and/or unresectable NET and currently on lanreotide therapy for at least 4 months were included in the study. A ^{68}Ga-DOTATATE PET/CT scan was performed on the day before and the day after lanreotide injection. In each patient ^{68}Ga-DOTATATE uptake ($SUV_{max, mean, peak}$) was assessed in both tumour lesions and normal tissue. All scans were assessed by two blinded nuclear medicine physicians for visual analysis. Paired T-tests were performed to determine the differences between the scans.

Results Of the 34 patients included, 31 were available for analyses in which 190 tumour lesions were measured. Uptake of ^{68}Ga-DOTATATE in tumour lesions was increased significantly after lanreotide, but decreased significantly in the liver, spleen, and thyroid gland resulting in a higher tumour-to-liver ratio.

Conclusion Lanreotide injection prior to ^{68}Ga-DOTATATE PET/CT does not result in decreased tumour uptake. In contrast, tumour uptake was increased, whereas the uptake in normal organs is decreased, leading to an increased tumour-to-liver ratio. However, these differences were small and not deemed clinically relevant. These results strongly suggest that discontinuation of lanreotide injections in the weeks prior to ^{68}Ga-DOTATATE PET examinations is unnecessary and does not compromise nuclear medicine imaging results.

Keywords Neuroendocrine Tumours · ^{68}Ga-DOTATATE · PET/CT · Lanreotide

Introduction

Neuroendocrine tumours (NET) are a heterogeneous group of rare cancers that represent only 2% of all malignancies [1]. During recent decades, the incidence of a NET has increased from 1.09 per 100,000 people in 1973 to 6.98 per 100,000 in 2012 in the United States [2]. NET arise from neuroendocrine cells anywhere throughout the body but the most common location is in the gastroenteropancreatic tract [3]. Although heterogeneous, almost all NET are characterized by an (over) expression of the somatostatin receptor (SSTR) of which five subtypes are known. Of these subtypes, $SSTR_2$ and $SSTR_5$ are most often expressed in NET [4]. The SSTR is utilized as a target for first-line therapy for the treatment of symptoms and tumour control of NET with somatostatin analogues (SSA) such as octreotide and lanreotide, which have a high affinity for $SSTR_2$ and $SSTR_5$ in metastatic midgut NET [5, 6].

The SSTR can also be used for diagnostic imaging. In that case, a somatostatin analogue is coupled to ^{111}In for SPECT

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imaging or ^{68}Ga for PET imaging [7]. The three main radiopharmaceuticals used for SSTR imaging by PET are ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC, and ^{68}Ga-DOTATOC. A meta-analysis on the performance of SSA PET/CT in NET, showed a sensitivity of 93% and a specificity of 96% [8].

Since both therapy with non-radiolabelled SSA and PET imaging with labelled ^{68}Ga-SSA involve binding to the same receptors, it is assumed that the uptake of ^{68}Ga-SSA is decreased due to receptor internalization and/or saturation from high-dose non radiolabelled SSA therapy [9, 10]. This assumption has even led to the recommendation that long-acting SSA treatment should be withdrawn 3-4 weeks prior to acquiring a ^{68}Ga-SSA PET scan in order to ensure tumour uptake [11].

Up to now, only two studies with octreotide evaluated the effect of SSA administration on the uptake of ^{68}Ga-DOTATATE. Both studies demonstrated that octreotide does not diminish tumour uptake of ^{68}Ga-DOTATATE. However, in one study the intra-individual comparison was only possible in a small subgroup of patients (9/105) and in the other study the time interval between the scan prior to and after octreotide was 9.6 ± 7.2 months as they compared a scan of treatment naïve patients to a scan after start of therapy. Therefore, tumour response or progression could not be excluded [12, 13].

The aim of the present study, therefore, was to prospectively assess the effect of lanreotide on the uptake of ^{68}Ga-DOTATATE intra-individually by comparing the scan 1 day prior to lanreotide injection to the scan 1 day after lanreotide injection.

Materials and methods

Patients

This prospective clinical study was performed at the Netherlands Cancer Institute in Amsterdam, the Netherlands. The study was approved by the Medical Ethics Committee (NL45948.031.13) and all patients provided written informed consent. Eligible patients were aged 18 years or older, had histologically confirmed well differentiated NET (grade I-II) that was treated with lanreotide (Ipsen, France) for at least 4 months, measurable disease ≥1 cm on ^{68}Ga-DOTATATE PET/CT, WHO performance status ≤2, and a life expectancy of at least 3 months. Patients were excluded in case of pregnancy or claustrophobia.

Study protocol

^{68}Ga-DOTATATE PET/CT imaging was performed 1 day prior and 1 day after lanreotide administration. The lanreotide injection was given at the regular dose (standard clinical dosages of 60, 90, or 120 mg) and time (every 3-4 weeks) for the individual patients and was administered by the family physician or home care nurse per regular protocol. A study team member contacted the family physician or home care nurse prior the administration of lanreotide to ensure that the injection was given on the day between the PET scans.

Sample size calculation

The day-to-day variation in the tumour uptake of ^{68}Ga DOTATATE is unknown, but assumed to be in the range of 0-10%, which is considered normal for other PET tracers. In a smaller similar study, Janson et al. compared the uptake of ^{111}In-octreotide before and after 12 months of treatment with lanreotide in a small group of patients ($n = 8$). The tumour-to background ratio increased on average 50% (range − 79 to 1087%) [14]. Based on this concept, a power-analysis was performed for the current study with a non-inferiority design. To measure an effect size of 0.5 in tumour-to-background ratio (80% power; two-sided alpha of 0.05), 34 patients were required for this study.

^{68}Ga-DOTATATE preparation

Fully automated labelling of ^{68}Ga-DOTATATE was performed using a labelling system (Scintomics GmbH, Germany) and sterile single-use cassettes (ABX GmbH, Germany). The peptide used was GMP grade DOTA-3-iodo-Tyr3-octreotate (ABX GmbH, Germany) with counterion acetate salt, purity >96%, and the packaged quantity was within 20% of the required quantity of peptide. In short, ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga generator (iThemba Labs, IDB Holland, the Netherlands; Galliapharm, Eckert & Ziegler, Germany; ITG, Germany) with hydrochloric acid. The eluate was added to 20-50 μg peptide and heated for 10 min at 100 °C. Quality control was performed with instant thin-layer chromatography and solid phase chromatography, which was validated with the quality control method provided by the European Pharmacopoeia for ^{68}Ga-Edotreotide. Batches were released for clinical usage if ^{68}Ga ions were < 2% and ^{68}Ga colloids <3% of the final product. Peptide amount per patient was calculated with the amount of peptide at the start of production, the total amount of radiolabeled peptide produced and the individual patient activity administered.

PET/CT imaging

PET/CT scans were performed approximately 45 min post injection of 100 MBq ^{68}Ga-DOTATATE from base of skull to mid-thigh; the sequential scans were performed at initial uptake time ± 5 min. Acquisitions were obtained on a Gemini ToF PET/CT (Philips, the Netherlands) with 2-2.5 min per bed position. A low-dose CT scan was acquired for attenuation correction and anatomical correlation.

Visual analysis

Visual analysis was performed by two nuclear medicine physicians with extensive experience with ^{68}Ga-DOTATATE PET/CT. Both physicians were blinded to which scans were pre- and post-lanreotide injection. A consensus was reached on which scan was preferred visually (scan 1, scan 2, or no preference). Furthermore, the number of lesions that were only visible on either one of the scans were determined.

Image quantification

SUV_{max}, SUV_{peak}, and $SUV_{mean50\%}$ were quantified in tumour lesions and normal organ tissue using the Metavol software (University of California, USA). Tumour lesions were categorized according to anatomical site as: primary, abdominal (including lymph nodes), lymph nodes (not in the abdomen), liver, lung, bone, other. The three visually most intense lesions in each category were quantified in each patient when available. Normal organ uptake was measured in liver, spleen, kidney, bone marrow, and adrenal, pituitary, parotid, and thyroid glands. When possible the organ was automatically segmented using $SUV_{50\%max}$. If auto segmentation could not be performed a spherical VOI of 1 cm^3 was placed in the organ. In those cases SUV_{peak} was not determined as it would be equal to SUV_{mean}. In case of diffuse liver metastases, no uptake in normal parenchyma was measured since these measurements were considered unreliable. Tumour-to-liver ratio was calculated as this was deemed the most clinically relevant due to the physiological high uptake of ^{68}Ga-DOTATATE and the frequent presence of NET metastases in the liver. This was calculated by dividing the SUV_{max} or SUV_{mean} of the tumour by the corresponding SUV_{max} or SUV_{mean} of the liver.

Statistical analysis

For image quantification paired T-tests were performed to determine whether or not there were significant differences in uptake of ^{68}Ga-DOTATATE between the two scans. Data are expressed as mean ± standard deviation (SD), with a p-value of <0.05 considered significant. When less than ten measurements were available no statistical analysis was done. Analyses were performed in SPSS v22 (IBM, USA) and graphs were produced in GraphPad Prism v7.03 (GraphPad Software Inc., USA).

Results

Patients and PET imaging

Thirty-four patients were included in this study. Patient demographics are shown in Table 1. Three patients did not undergo the second scan; in one instance the radiopharmaceutical did not pass quality control, one patient was reported to be treated with lanreotide, but this was not the case, and one patient failed to appear at the second appointment. The average injected activity and time between scan and injection were not significantly different between scan 1 (89.59 MBq, 47.8 min) and scan 2 (91.98 MBq, 48.9 min) and are shown in Fig. 1. Peptide mass was identical between scan 1 and scan 2 (7.39 ± 4.10 μg vs 7.65 ± 4.34 μg, $p = 0.649$). ^{68}Ga ions (mean ± SD 0.73 ± 0.41%) and ^{68}Ga colloids (mean ± SD 1.47 ± 0.56%) were within limits.

Table 1 Demographics of the 34 patients included in this study. Data is shown as absolute number (percentage) or as mean (range). * for 33 patients, 1 patient was excluded for not receiving lanreotide

Gender	Male	21 (61.8%)
	Female	13 (38.2%)
Age (years)		64.2 (45-78)
Primary tumour site	Small bowel	24 (70.6%)
	Pancreas	4 (11.8%)
	Caecum	2 (5.9%)
	Rectum	1 (2.9%)
	Unknown primary	3 (8.8%)
Grade	I	22 (64.7%)
	II	12 (35.3%)
Lanreotide dose (mg)*	60	2 (5.9%)
	90	13 (38.2%)
	120	18 (52.9%)

Visual analysis

Visually, the preferred scan was pre-lanreotide in two cases (6%) and post-lanreotide in 13 cases (42%), while in 16 cases (52%) it was ambiguous. Preference was most often caused by lower liver uptake leading to better visibility of tumour lesions in the liver. On the scans performed before lanreotide injection 16 lesions were not identified, 14 in the liver and two in the bone. On the scans performed after lanreotide injection six lesions were not identified, equally divided between liver and bone. The visualisation of the additional lesions on either scan did not have a clinical impact in any of the patients.

Tumour uptake

One hundred and ninety tumour lesions were quantified in 31 patients. In general, SUV_{max} significantly increased in tumour lesions after lanreotide injection [20.96 vs. 21.64 (prior vs. post lanreotide), $p = 0.034$] while SUV_{peak} (16.45 vs. 16.86, p = NS) and SUV_{mean} (14.77 vs. 15.03, p = NS) remained relatively unchanged. Although uptake significantly increased, this difference is not deemed clinically relevant. Subgroup analyses could be performed for metastatic lesions in the abdomen, liver, lymph nodes, bone, and other. Only the SUV_{peak}

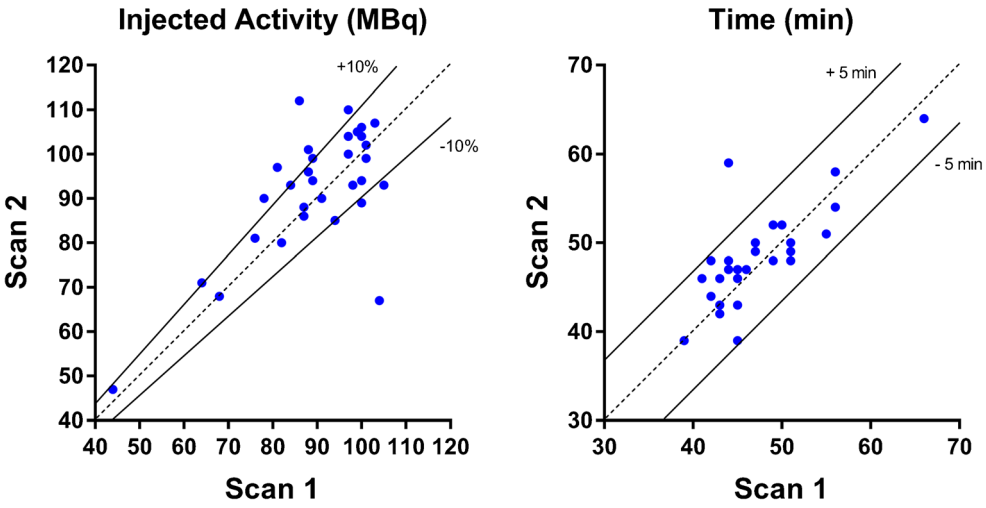

Fig. 1 Injected activity and time post injection for each patient. Scan 1 is prior to lanreotide injection and scan 2 after lanreotide injection. The dotted diagonal line represents equal parameters for both scans. The solid lines are the optimal range of deviation between the two scans; ±10% for injected activity and ± 5 min for time post-injection

(16.96 vs. 18.06, $p = 0.047$) and SUV_{mean} (15.38 vs. 16.55, $p = 0.025$) in abdominal lesions was significantly higher after lanreotide. No other significant differences were found. All data is shown in Table 2 and Fig. 2A shows the SUV_{max} on the second scan as percentage of the first scan.

Normal tissue uptake

Contrary to tumour uptake, SUV_{max} in normal tissue significantly decreased after lanreotide injection; in the liver [10.15 vs. 9.08 (prior vs. post lanreotide), $p < 0.001$],

Table 2 SUV_{max}, SUV_{peak}, and SUV_{mean} for tumour lesions (mean ± SD). Paired differences for scan 1 - scan 2 (mean ± SD). nd = not determined. * = significant ($p < 0.05$)

Tumour		Scan 1 Before lanreotide	Scan 2 After lanreotide	Paired difference	*p*-value
All lesions $n = 190$	SUV_{max}	20.96 ± 12.37	21.64 ± 12.63	−0.67 ± 4.35	0.034 *
	SUV_{peak}	16.45 ± 10.92	16.86 ± 11.22	−0.41 ± 2.99	0.076
	SUV_{mean}	14.77 ± 8.57	15.03 ± 8.69	−0.25 ± 2.86	0.254
Primary $n = 4$	SUV_{max}	28.87 ± 13.98	32.66 ± 16.19	nd	nd
	SUV_{peak}	24.05 ± 12.73	26.63 ± 13.32	nd	nd
	SUV_{mean}	19.20 ± 9.72	21.12 ± 10.29	nd	nd
Abdominal $n = 28$	SUV_{max}	22.61 ± 13.11	24.49 ± 13.52	−1.88 ± 4.87	0.052
	SUV_{peak}	16.96 ± 10.57	18.06 ± 10.72	−1.10 ± 2.44	0.047 *
	SUV_{mean}	15.38 ± 8.78	16.55 ± 8.73	−1.17 ± 2.97	0.025 *
Liver $n = 64$	SUV_{max}	26.20 ± 10.66	26.77 ± 11.14	−0.57 ± 4.95	0.356
	SUV_{peak}	24.28 ± 9.00	24.58 ± 10.03	−0.30 ± 4.23	0.671
	SUV_{mean}	19.80 ± 6.83	19.59 ± 7.59	0.21 ± 3.36	0.633
Lymph nodes $n = 46$	SUV_{max}	18.13 ± 12.80	18.85 ± 12.17	−0.72 ± 3.95	0.223
	SUV_{peak}	13.99 ± 10.65	14.43 ± 10.32	−0.45 ± 2.55	0.208
	SUV_{mean}	13.05 ± 8.82	13.58 ± 8.45	−0.53 ± 2.65	0.271
Bone $n = 32$	SUV_{max}	16.79 ± 11.05	15.92 ± 10.67	0.88 ± 3.29	0.142
	SUV_{peak}	11.33 ± 8.40	10.76 ± 8.08	0.57 ± 1.91	0.098
	SUV_{mean}	11.79 ± 7.74	11.09 ± 7.38	0.71 ± 2.34	0.103
Lung n = 6	SUV_{max}	11.50 ± 11.34	11.13 ± 10.23	nd	nd
	SUV_{peak}	7.62 ± 8.42	7.81 ± 8.44	nd	nd
	SUV_{mean}	7.69 ± 7.35	7.65 ± 7.11	nd	nd
Other n = 10	SUV_{max}	11.76 ± 6.27	13.84 ± 9.57	−2.08 ± 3.59	0.100
	SUV_{peak}	7.70 ± 4.65	8.98 ± 6.64	−1.28 ± 2.30	0.109
	SUV_{mean}	8.08 ± 4.28	9.40 ± 6.40	−1.32 ± 2.34	0.112

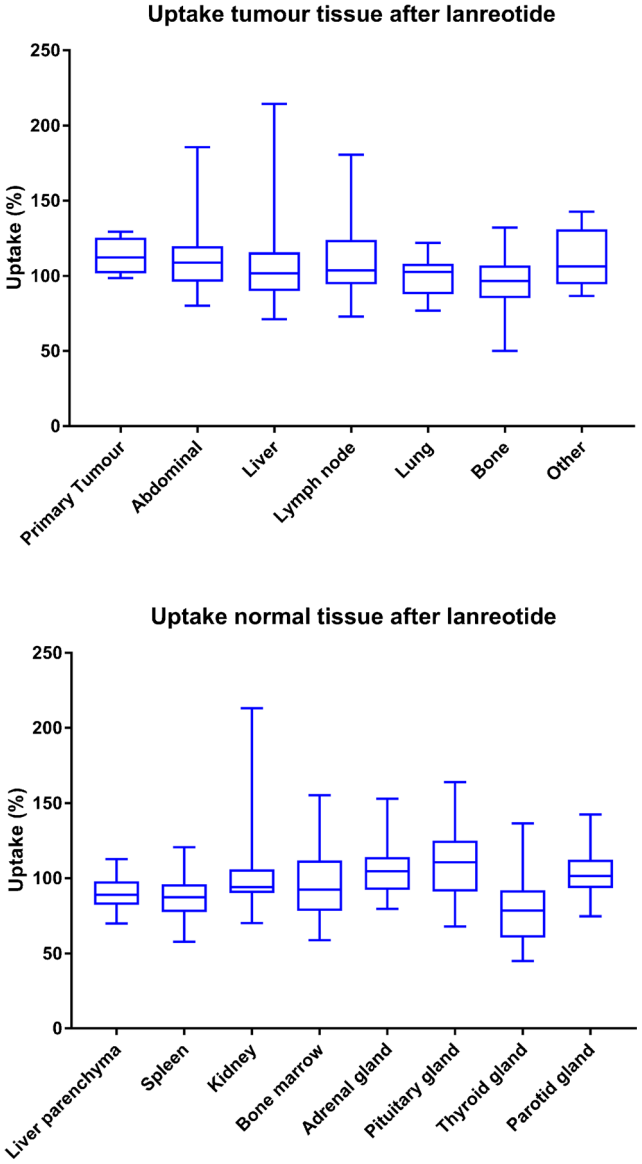

Fig. 2 Percentage of uptake of ^{68}Ga-DOTATATE after lanreotide compared to before lanreotide in (A) tumour lesions and (B) normal organ tissue. Box plots indicate the median, 25th and 75th percentile, and minimum and maximum values

spleen (25.77 vs. 22.35, $p < 0.001$), and thyroid gland (4.13 vs. 3.14, $p < 0.001$). The same held true for the SUV_{mean} in the liver (8.80 vs. 7.87, $p < 0.001$), spleen (23.07 vs. 20.11, $p < 0.001$), and thyroid gland (3.15 vs. 2.47, $p < 0.001$). In the kidney, bone marrow, and adrenal, pituitary, and parotid glands, no significant differences were seen in either SUV_{max}, SUV_{peak}, or SUV_{mean}. All data are shown in Table 3 and Fig. 2B shows the SUV_{max} on the second scan as percentage of the first scan (Table 4).

Tumour-to-liver ratio

The tumour-to-liver ratio for SUV_{max} increased after lanreotide injection in all lesions [2.21 vs. 2.59 (prior vs. post lanreotide), $p < 0.001$], in abdominal (2.58 vs. 3.09, $p = 0.002$), liver (2.80 vs. 3.18, $p < 0.001$), lymph node (1.77 vs. 2.16, $p < 0.001$), as well as in bone (1.89 vs. 2.18, $p = 0.012$) lesions. The tumour-to-liver ratio of SUV_{mean} increased after lanreotide injection in all lesions (1.83 vs. 2.11, $p < 0.001$); abdominal (2.02 vs. 2.40, $p = 0.001$), lymph node (1.4 vs. 2.77, $p < 0.001$), as well as in bone (1.51 vs. 1.77, $p = 0.003$) lesions.

Discussion

This study evaluates the effect of lanreotide on the uptake of ^{68}Ga-DOTATATE. It is the first prospective intra-individual comparison study in which both the time interval between the injection of the somatostatin analogue and ^{68}Ga-DOTATATE (1 day) and the interval between the pre- and post-lanreotide scans (2 days) remained were standardized.

Because of utilization of the SSTR by SSAs for both therapy and imaging, it is currently recommended to discontinue long-acting SSAs prior to imaging [11]. Although the older guideline from 2010 explains that this issue is still up to debate and not standard clinical protocol in all centres [15], in the current guideline uncertainties are omitted and recommendations are based solely on one published clinical study [16]. In that study, ^{68}Ga-DOTATOC uptake is measured after intravenous injection of different dosages of octreotide (0, 50, 250, 500 μg) in nine patients. Interestingly, they conclude that tumour-to-background ratio is highest after pre-administration of 50 μg of octreotide in 5/6 patients [16].

As long ago as 1993, clinical studies have been published that investigate whether or not non-radiolabelled SSAs influence the uptake of radiolabelled SSAs. Dörr et al. showed in two small trials ($n = 5$ and $n = 10$, resp.) that tumour visualization with ^{111}In-pentetreotide scintigraphy improved during treatment with SSAs and that tumour detection, including liver metastases, might be improved during SSA therapy. Based on these small cohorts it was also concluded that the biodistribution changed significantly during SSAs treatment, with decreased spleen (25-63%), hepatic (50-84%) and renal (72-88%) accumulation [17, 18]. In 1999, Janson et al. investigated 8 NET patients with ^{111}In-pentetreotide scintigraphy prior and during lanreotide treatment, and showed an average increase of tumour-to-background uptake of 50% (−79% to +1087%) during SSA treatment [14].

These three studies have very small patient numbers with large standard deviations and were performed before the introduction of ^{68}Ga-SSA PET/CT. More recently, two reports on the effect of octreotide on the uptake of ^{68}Ga-DOTATATE were published [12, 13]. The first study compared the ^{68}Ga-DOTATATE PET/CT scans in 35 patients under treatment with octreotide to 70 patients without octreotide and performed an

Table 3 SUV_{max}, SUV_{peak}, and SUV_{mean} for normal tissue (mean ± SD). Paired differences for scan 1 - scan 2 (mean ± SD). nd = not determined. * = significant ($p < 0.05$)

Normal tissue		Scan 1 Before lanreotide	Scan 2 After lanreotide	Paired difference	*p*-value
Liver parenchyma *n* = 27	SUV_{max}	10.15 ± 2.26	9.08 ± 2.34	1.07 ± 1.06	<0.001 *
	SUV_{peak}	nd	nd	nd	nd
	SUV_{mean}	8.80 ± 2.04	7.81 ± 1.93	1.0 ± 0.95	<0.001 *
Spleen n = 31	SUV_{max}	25.77 ± 7.60	22.35 ± 7.34	3.42 ± 3.57	<0.001 *
	SUV_{peak}	nd	nd	nd	nd
	SUV_{mean}	23.07 ± 6.90	20.11 ± 6.64	2.96 ± 3.27	<0.001 *
Adrenal gland n = 29	SUV_{max}	19.20 ± 4.50	20.55 ± 6.49	−1.35 ± 3.62	0.054
	SUV_{peak}	14.53 ± 3.07	15.13 ± 4.18	−0.60 ± 2.41	0.236
	SUV_{mean}	13.23 ± 3.03	13.89 ± 4.24	−0.66 ± 2.42	0.153
Pituitary gland *n* = 27	SUV_{max}	6.57 ± 2.38	7.07 ± 2.47	−0.50 ± 1.34	0.062
	SUV_{peak}	3.99 ± 1.40	4.17 ± 1.39	−0.18 ± 0.77	0.230
	SUV_{mean}	4.64 ± 1.72	4.98 ± 1.71	−0.34 ± 0.91	0.067
Parotid gland *n* = 29	SUV_{max}	3.99 ± 1.58	4.18 ± 2.05	−0.20 ± 0.83	0.213
	SUV_{peak}	3.74 ± 1.37	4.05 ± 2.09	−0.31 ± 0.93	0.257
	SUV_{mean}	3.03 ± 1.18	3.18 ± 1.52	−0.16 ± 0.66	0.205
Thyroid gland *n* = 26	SUV_{max}	4.13 ± 2.17	3.14 ± 1.71	0.99 ± 1.01	<0.001 *
	SUV_{peak}	nd	nd	nd	nd
	SUV_{mean}	3.15 ± 1.71	2.47 ± 1.41	0.68 ± 0.73	<0.001 *
Kidney n = 31	SUV_{max}	19.75 ± 5.18	20.66 ± 9.75	−0.91 ± 7.32	0.493
	SUV_{peak}	nd	nd	nd	nd
	SUV_{mean}	12.95 ± 3.43	13.72 ± 5.24	−0.77 ± 3.45	0.222
Bone marrow n = 31	SUV_{max}	2.39 ± 0.62	2.23 ± 0.58	0.16 ± 0.53	0.092
	SUV_{peak}	nd	nd	nd	nd
	SUV_{mean}	1.48 ± 0.42	1.84 ± 2.12	−0.36 ± 2.15	0.356

intra-individual comparison in 9 patients. They found no significant difference in SUV_{max} or SUV_{mean} of both the primary tumour or any metastases between the two groups, but a decrease in average uptake in the liver (6.6 ± 1.9 vs. 4.9 ± 1.4, $p < 0.001$) and spleen (18.2 ± 5.0 vs. 12.8 ± 4.4, $p < 0.001$) after octreotide treatment [12]. The main drawback of this study are its retrospective nature, the variety in time between octreotide administration and PET/CT (14.5 ± 11.4 days), and the small sample with an intra-individual comparison in which the time between the two scans was 13.8 ± 15.6 weeks. The latest report performed an intra-individual comparison of ^{68}Ga-DOTATATE PET/CT in 30 patients prior to and during octreotide treatment. Again, it was shown that octreotide decreased the uptake in normal tissues (liver, spleen, thyroid), but not in primary tumours or metastatic lesions [13]. This study however also had a retrospective design in which the time between the two PET/CT scans was 9.6 ± 7.2 months and the time between octreotide injection and PET/CT was 25.1 ± 14.8 days. Therefore, progression or response might have occurred in between and octreotide concentration was variable between patients. Furthermore, a small study in five patients compared uptake of ^{68}Ga-DOTATOC before and directly after ^{177}Lu-DOTATATE administration found no evidence of receptor saturation in tumours [19].

In our prospective, well standardized study only a few lesions were visible on either one PET/CT (prior to or after lanreotide administration), though in none of the patients this had impact on clinical staging or decision making. Additionally, no clinically relevant changes in tumour SUVs were observed between ^{68}Ga-PET/CT 1 day prior and 1 day after lanreotide injection (20.96 vs. 21.64, $p = 0.034$). The uptake in normal liver parenchyma, spleen and thyroid gland did show significant decreases after lanreotide injection, as was also described in the previous studies. Consequently, the derived value tumour-to-liver ratio also increased after lanreotide injection in all lesions (2.21 vs 2.59, $p < 0.001$). Given that the pharmacokinetic profile of lanreotide shows a maximal concentration within 1 day after injection with a gradual elimination

Table 4 Tumour-to-liver ratio. nd = not determined. * = significant ($p < 0.05$)

Tumour		Scan 1 Before lanreotide	Scan 2 After lanreotide	*p*-value
All lesions *n* = 165	Ratio SUV_{max}	2.21	2.59	<0.001 *
	Ratio SUV_{mean}	1.83	2.11	<0.001 *
Primary n = 3	Ratio SUV_{max}	2.76	3.10	nd
	Ratio SUV_{mean}	2.26	2.49	nd
Abdominal n = 26	Ratio SUV_{max}	2.58	3.09	0.002 *
	Ratio SUV_{mean}	2.02	2.40	0.001 *
Liver *n* = 52	Ratio SUV_{max}	2.80	3.18	<0.001 *
	Ratio SUV_{mean}	2.66	2.86	0.093
Lymph nodes *n* = 41	Ratio SUV_{max}	1.77	2.16	<0.001 *
	Ratio SUV_{mean}	1.44	1.77	<0.001 *
Bone n = 27	Ratio SUV_{max}	1.89	2.18	0.012 *
	Ratio SUV_{mean}	1.51	1.77	0.003 *
Lung n = 6	Ratio SUV_{max}	1.22	1.25	nd
	Ratio SUV_{mean}	0.88	1.01	nd
Other n = 10	Ratio SUV_{max}	1.24	1.75	0.080
	Ratio SUV_{mean}	0.97	1.31	0.091

phase, it has to be emphasized that present differences resemble the worst-case scenario [20, 21]. Therefore, it can be concluded that the effect of lanreotide treatment on the diagnostic accuracy for the detection and quantification of NET lesions is very limited. However, since a small change in tumour-to-liver ratio is demonstrated, clinicians need to be aware of this when using ^{68}Ga-DOTATATE PET/CT for response monitoring. Nevertheless, this study again underlines that the accuracy for the detection of liver lesions increases rather than decreases directly after lanreotide injection.

This study has several limitations and premises, which will be addressed: the use of high affinity DOTATATE, the presence of a low dose of lanreotide in the control group, the timing of the scan after lanreotide, and three patients that dropped out of the study. This study has been performed with high affinity DOTATATE whilst the most commonly used peptide is DOTATATE. We do not expect this to influence the results as the both peptides have been compared and the investigators concluded that there were no differences in uptake in mayor organs or tumour lesions [22]. In this study the control group has a low plasma dose of lanreotide. The study was designed this way since this represents the clinical situation in which patients are under treatment with a somatostatin analogue and cannot be withheld until the plasma levels are undetectable, which is at least 90 days [21]. We do not expect this to influence the results since the concentration remaining is several times lower than the peak concentration. This study assumes that peak tissue concentration and receptor binding of lanreotide is reached within 1 day. Although the tissue binding profile of lanreotide is unknown, this premise is based on two known parameters. The first is that the maximum concentration of lanreotide in plasma is reached within a day of intramuscular injection [21]. The second is that receptor binding occurs very fast after introduction of lanreotide in the blood. This is supported by data from studies with 177Lu-DOTATATE, which show that maximum tumour uptake is reached within several hours after intravenous administration [23] and by pharmacokinetic modelling [24]. Since this study examines the maximum achievable difference in lanreotide plasma concentration, it is expected to be generalizable to all other time points. Finally, three patients dropped out of the study which led to the samples size not being reached. However, even with fewer patients ($n = 31$ with 190 tumour lesions) a small difference was demonstrated. Therefore, we do not expect a dropout rate of <10% to influence the results.

If long-acting somatostatin analogues such as lanreotide can be continued during ^{68}Ga-SSA PET/CT examinations, this is of major benefit for both the patient and the nuclear medicine department. Patients will no longer have to extend the duration between SSA administration and the PET/CT or switch to short-acting SSAs that have to be administered three times daily. For nuclear medicine departments this ensures that ^{68}Ga-SSA PET/CT patients can be clustered and examinations performed at any time without observing each patients' personal SSA administration schedule.

A question that remains unanswered is the effect of non-radiolabelled SSAs on the uptake of ^{177}Lu- or ^{90}Y-SSAs for peptide receptor radionuclide therapy (PRRT). Since the amount of peptide administered during PRRT is approximately 10× higher than for ^{68}Ga-SSA PET, the results of this study should not be extrapolated without further research to PRRT.

Conclusion

Whether somatostatin analogues should be discontinued prior to somatostatin receptor imaging has been debated for many years. The present study demonstrates that administration of lanreotide prior to ^{68}Ga-DOTATATE leads to similar or increased tumour uptake, decreased or equal normal tissue uptake, and an increased tumour-to-liver ratio. These results strongly suggest that discontinuation of SSAs prior to somatostatin receptor imaging is unnecessary and that therapy can be continued without compromising the outcomes of nuclear medicine imaging.

Compliance with ethical standards

Disclosure statement This research was supported by an unrestricted grant from Ipsen. Ipsen was not involved in the conduct of the study or the drafting of the manuscript, but did complete a courtesy review of the final version before submission.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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