The Influence Of Long Acting Somatostatin Analogue Therapy On ^{68}GA-DOTATATE Uptake In Patients With Neuroendocrine Tumours: A Retrospective Study

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ABSTRACT

INTRODUCTION Somatostatin analogues (SSAs) are often used for the treatment of neuroendocrine tumours (NET). Both tumour imaging with ^{68}Ga-DOTATATE and SSA therapy utilize the same receptor. Current guidelines recommend a 3-4 week interval between SSA treatment and ^{68}Ga-DOTATATE PET/CT imaging. The aim of this study is to investigate the effect of long acting SSA use on ^{68}Ga-DOTATATE uptake (SUV_{max}) in the primary tumour lesions and normal liver tissue in patients diagnosed with NET.

METHODS 288 ^{68}Ga-DOTATATE PET/CT scans from the period 2016-2022 were evaluated. Scans were divided into two groups: non-users and users of long-acting SSA prior to the PET/CT scan. Differences in ^{68}Ga-DOTATATE uptake (SUV_{max}) in the primary tumour lesions, physiological SUV_{max} in the liver and tumour-to-liver ratio between the two groups were compared to draw result.

RESULTS Long-acting SSA users showed a significant increase of the SUV_{max} in the primary tumour compared to the non-treatment group (30.51 ± 1.83 vs 22.55 ± 2.02; $p = 0.005$). Moreover, there was a significant lower physiological uptake in the liver of patients with SSA treatment compared to non-users (8.98 ± 1.35 vs 10.47 ± 1.39; $p < 0.001$). Tumour-to-liver ratio in SSA users was also significantly increased (3.42 ± 1.83 vs 2.12 ± 1.97; $p < 0.001$).

CONCLUSION Treatment with long-acting SSAs significantly increases tumour uptake of ^{68}Ga-DOTATATE and tumour-to-liver ratio, while decreasing physiological liver uptake. These findings could have further implications for the current guidelines that recommend to discontinue SSA treatment weeks prior to ^{68}Ga-DOTATATE imaging.

KEY WORDS: ^{68}Ga-DOTATATE; neuroendocrine tumours; PET/CT; somatostatin analogues; octreotide; lanreotide; somatostatin receptor imaging

INTRODUCTION

Neuroendocrine tumours (NET) are a relatively rare and heterogeneous group of tumours. They have an incidence of approximately 1 to 5 per 100.000 people *(1)*. These type of tumours can show up in any neuroendocrine organ, but mainly arise in the gastrointestinal tract, lungs and pancreas *(2)*. Most of these tumours show an overexpression of somatostatin receptors (SSTR) on the cell surface, which these tumours are characterized by *(3)*. There are five subtypes of SSTR characterized, in which $SSTR_2$ and $SSTR_5$ have the highest expression in NET *(4)*. Due to the high expression of SSTR, synthetic somatostatin analogues (SSA) such as octreotide and lanreotide are used for symptomatic control and to delay disease progression. Octreotide and lanreotide mainly bind to $SSTR_2$ *(5)*. Somatostatin analogues usually have a short half-life, however long-acting depot preparations have been developed due to patient convenience *(6)*. Long-acting octreotide (Sandostatine LAR, Novartis, Switzerland) and long-acting lanreotide (Somatuline, Ipsen, France) are currently approved for treatment of NET.

The SSTR overexpression in NETs also make these tumours suitable for ^{68}Ga-DOTATATE PET/CT imaging. ^{68}Ga-DOTATATE (^{68}Ga-DOTA-octreotate) consists of radiolabelled SSA and is used for staging, restaging and to determine whether patients are suitable for peptide receptor radionuclide therapy (PRRT). This makes ^{68}Ga-DOTATATE essential in NET management *(7)*. PRRT with ^{177}Lu-DOTATATE (^{177}Lu-DOTA-octreotate) consist of radioactive labelled SSA and has shown to be a significant treatment for patients with NETs *(8, 9)*. ^{68}Ga-DOTATATE can be used as a predictive marker for the effectiveness of PRRT, since the effectiveness of PRRT correlates to the amount of SSTR present on the tumour cell *(10)*.

Similar to the somatostatin analogues, ^{68}Ga-DOTATATE tracer also binds to $SSTR_2$ *(11)*. Therefore, there is a theoretical assumption that SSA use may lead to decreased ^{68}Ga-DOTATATE tumour uptake and detection *(12)*. This may lead to confounded interpretation of the ^{68}Ga-DOTATATE imaging data *(13)*. The manufacturer therefore advises to image patients with ^{68}Ga-DOTATATE prior to administration of long-acting SSAs *(14)*. The European Association of Nuclear Medicine also recommends an interval of 3 to 4 weeks between long-acting SSA administration and ^{68}Ga-DOTA-conjugated peptides PET/CT, however there is no clear evidence for this discontinuation *(15)*. There are a limited number of studies that suggest that there is no decrease ^{68}Ga-DOTATATE tumour uptake and rather demonstrate an improved tumour-to-background ratio *(16-20)*. More evidence is needed to evaluate whether the recommendation to discontinue SSA treatment before a Ga-68 DOTATATE PET/CT scan is justified.

The aim of this study is to investigate the effect of long-acting SSA use on ^{68}Ga-DOTATATE uptake (SUV_{max}) in the primary tumour lesions and normal liver tissue in patients diagnosed with NET.

METHODS

Patients

This study was retrospectively conducted at the Amsterdam University Medical Centre, location AMC, the Netherlands. This study was approved by the Medical Ethics Assessment Committee. Patients where eligible to be included if they had received a ^{68}Ga-DOTATATE PET/CT scan during the period 2016-2022, were active or earlier diagnosed with NET and were at least 18 years old at the time of the scan. Each PET/CT scan was considered as an individual case.

Patients were divided into two groups based on medication use. First group consisted of patients who were non-users of long-acting SSA at the time of ^{68}Ga-DOTATATE imaging. Second group consisted of patients who were under treatment of a long-acting SSA at the time of ^{68}Ga-DOTATATE imaging. Patients where considered to be under treatment if they had at least one dose of SSA (long-acting octreotide or long-acting lanreotide) administered in the last 3 months before the date of the PET/CT scan.

We performed a sub-analysis to view the effect of the octreotide and lanreotide on ^{68}Ga-DOTATATE uptake separately. To assess whether the time between last administration of the SSA and the moment of the scan would show any different effect, we also performed a second sub-analysis. Patients were divided into 3 subgroups for this sub-analysis. First group consisted of patients without SSA use at the time of ^{68}Ga-DOTATATE treatment. Second group consisted of patients who were under treatment of a long-acting SSA at the time of ^{68}Ga-DOTATATE treatment, where the last moment of SSA administration prior to the PET/CT was no longer than 4 weeks ago. Third group consisted patients who were under treatment of a long-acting SSA at the time of ^{68}Ga-DOTATATE treatment, where the last moment of SSA administration prior to the PET/CT scan was between 4 weeks and 3 months ago.

Differences in SUV_{max} in the primary tumour-to-background, difference in SUV_{max} in liver-to-background and difference in tumour-to-liver ratio between the groups were reviewed to draw result for all three analysis. The tumour-to-liver ratio is especially relevant as NET often metastasizes to the liver *(21)*.

^{68}Ga-DOTATATE labelling procedure

First, 1.1 ml ^{68}Ga-solution in 0.1 M HCl was generated using a Ti02 based ^{68}Ge/^{68}Ga-generator (Galli Eo, IRE ELit, Belgium). Then, a sodium acetate buffer dilution was made from 5 ml European Pharmacopoeia (Ph. Eur.) sodium acetate buffer solution (Fischer Chemical, United Kingdom) and 95 ml NaCl 0.9%. Thereafter, 50 µg DOTATATE (ABX, Germany) was solved in 3 ml of this solution, added to the 1.1ml ^{68}Ga-solution and heated at 95°C for 7 minutes. Radiolabelling efficiency was measured using radio high-performance liquid chromatography. A radiolabelling efficiency of >91% was considered sufficient.

PET/CT scan procedure

Up to October 1, 2017 the Gemini TF (Philips Healthcare, Eindhoven, the Netherlands) was used. First, a diagnostic CT scan was performed from the thigh to the skull base (120 kV, 150 mAs, 16x1.5 collimation, 0.8013 pitch) during administration of 2 ml/kg intravenous contrast agent (iopromide 300 mg/ml, Ultravist 300; Bayer Healthcare Pharmaceuticals, Berlin, Germany) with a 2 ml/s flow and a 50s delay (portal phase). Then, the PET acquisition followed, with a scan time of 2.5 minutes per bed position and reconstructed in 5 mm slices and 4x4 mm pixels. After October 1, 2017 a Biograph mCT Flow (Siemens Medical Solutions, Erlangen, Germany) equipped with enhanced axial field of view (TrueV) scanner was used. A diagnostic CT scan was performed with automatic modulation in current and voltage. Reference values were set on 120 kV and 160 mA, 128x0.6 collimation and 0.9 pitch. CT scan was performed after administration of intravenous iodinated contrast medium (90 ml Xenetix 350; Guerbet, Roissy CdG Cedex, France) with a 3 ml/s flow and a 65s delay (portal phase). PET was performed with continuous bed motion at 1.5 mm/s in 3D acquisition mode. CT data was used for PET attenuation correction and PET data were reconstructed with TrueX algorithm (three dimensions ordered subsets expectation maximization iterative reconstruction with time of flight and point spread function compensation, 21 subsets, 2 iterations, and a 5 mm Gaussian post-filter) in 4 mm × 4 mm × 5 mm voxels**.**

PET/CT image acquisition was performed 45 to 60 minutes after intravenously injection of approximately 1.5 MBq/kg ^{68}Ga-DOTATATE. The patients were instructed to drink at least 500 mL of water and to urinate before the scan, to stimulate ^{68}Ga-DOTATATE excretion from the renal calyces.

PET/CT image analysis

PET/CT images were analysed using Hybrid Viewer software, Hermes Medical Solutions (version 5.1.0). SUV_{max} was calculated with correction for body weight, using a spherical volume of interest (VOI) tool. VOIs were drawn manually in the primary tumour, the liver and the left psoas major muscle. A VOI of 4 cm was used for the primary tumour and liver, and a VOI of 2 cm for the psoas major muscle. If there were multiple primary tumour lesions present, the most focal tumour (highest SUV_{max}) was chosen to calculate SUV_{max}. For the liver, the VOI was drawn in the right lower lobe for all patients, unless this wasn't possible due to a presence of metastases in the right lower lobe. Then the region of interest to calculate SUV_{max} was drawn elsewhere in the liver where no metastasis was present. The tumour-to-liver ratio was calculated by dividing the SUV_{max} of the primary tumour by the corresponding SUV_{max} of the liver. To calculate background uptake, the SUV_{max} of the left psoas major muscle was calculated for all patients. During the period of 2016 – 2022 two different scanners where used to perform PET/CT scans. To compensate for the possible difference in sensitivity between the two scanners, the SUV_{max}-to-background ratio was used to draw result. Where the SUV_{max} of the tumour lesion and liver was divided by the corresponding background uptake.

Statistical analysis

SPSS software (version 28, IBM, USA) was used to perform the statistical analysis. The unpaired t-test was used to assess the differences in SUV_{max} between the two main

Table 1: Patient characteristics of the study population

Characteristic	No SSA treatment	SSA treatment (<3 months)	*p*†
Sex			NS
Male (%)	116 (56.0%)	43 (53.1%)	
Female (%)	91 (44.0%)	38 (46.9%)	
Age (years)	63.2 ± 12.3	63.9 ± 11.5	NS
BMI	25.8 ± 4.8	25.2 ± 5.8	NS
Primary tumour location			NS
Pancreas (%)	89 (43.0%)	20 (24.7%)	
Stomach/Small intestines (%)	65 (31.4%)	47 (58.0%)	
Adrenal gland (%)	19 (9.2%)	2 (2.5%)	
Colon/Rectum (%)	11 (5.3%)	4 (4.9%)	
Cervix/Ovary (%)	6 (2.9%)	0 (0.0%)	
Lung (%)	5 (2.4%)	0 (0.0%)	
Other/Unknown (%)	12 (5.8%)	8 (9.9%)	
Presence primary tumour			NS
Resected (%)	85 (41.1%)	30 (37.0%)	
Present (%)	122 (59.9%)	51 (63.0%)	
Tumour Grade			NS
I (%)	85 (41.1%)	40 (49.4%)	
II (%)	75 (36.2%)	36 (44.4%)	
III (%)	9 (4.3%)	0 (0.0%)	
Unknown (%)	38 (18.4%)	5 (6.2%)	
Activity (MBq/kg)	1.5 ± 0.3	1.5 ± 0.3	NS
Peptide (ng/kg)	152.6 ± 76.2	145.1 ± 71.5	NS
Treatment			
Lanreotide (%)	NA	57 (70.3%)	
Octreotide (%)	NA	24 (29.7%)	
Last SSA injection (days)††	NA	29.33 ± 17.16	

NA = Not applicable

NS = No statistically significant difference

Continues data are displayed as mean ± SD, qualitative data are displayed as numbers with percentage in the parentheses

† Chi-square test was performed for qualitative variables and unpaired t-test for quantitative variables, $p < 0.05$ was considered statistically significant

†† Time (days) between last long-acting SSA administration and moment of ^{68}Ga-DOTATATE scan

groups and also for the first sub-analysis. One-way ANOVA was used to evaluate the differences in SUV_{max} between the three subgroups in the second sub-analysis. The SUV_{max} data were transformed using natural logarithm to achieve a normal distribution. To assess differences in patient characteristics between the two groups, Chi-square test was performed for qualitative variables and unpaired t-test for quantitative variables. All tests were 2-tailed and a *p*-value of <0.05 was considered as statistically significant.

RESULTS

Study population

A total of 200 patients were retrospectively reviewed in this study. This amounted to 288 PET/CT scans (159 men; 129 women; mean age 63.4 ± 12.1), since various patients had undergone multiple ^{68}Ga-DOTATATE PET/CT scans (Table 1). From the 288 scans, 115 scans involved scans where the primary tumour was resected. Hence it was not possible to determine a SUV_{max} of the primary tumour for these scans and to calculate a tumour-to-liver ratio. However, the SUV_{max} of the liver of these patients was still included. The stomach/small intestines (n = 112) was the most common primary tumour location followed by the pancreas (n = 109). There were no significant differences found in the characteristics of the patients between the two study groups. There was a total of 81 scans where the patient had used a long acting SSA-prior to the PET/CT scan. Further details can be found in Table 1.

Effect of SSA treatment on tumour lesion uptake

The SUV_{max} of 173 primary tumours (122 in the non-treatment group, 51 in the SSA treatment group) were quantified (Table 2). Overall, patients who had undergone SSA treatment showed a significant increase in the SUV_{max} of the primary tumour compared to the non-treatment group (30.51 ± 1.83 vs 22.55 ± 2.02; $p = 0.005$).

There were 35 primary tumours quantified in patients using lanreotide and 16 primary tumours in octreotide (Table 3). When looked at the different SSAs administered, both lanreotide (28.38 ± 1.89 vs 22.55 ± 2.02; $p = 0.070$) as octreotide (35.73 ± 1.66 vs 22.55 ± 2.02, $p = 0.003$) use showed an increase in SUV_{max} in the primary tumour lesion. However, only octreotide users showed a statistically significant increase as opposed to lanreotide users.

Effect of SSA treatment on physiological liver uptake

Table 2 shows that the physiological uptake of 288 livers were quantified (207 in the non-treatment group, 81 in the SSA treatment group). There was a statistically significant lower physiological uptake in the liver of patients with long-acting SSA treatment as opposed to the patients who had not undergone SSA treatment (8.98

Table 2: Overview of SUV_{max} values of the primary tumour and liver between no treatment and SSA treatment

Parameter	No SSA treatment	SSA treatment (<3 months)	*p*†
SUV_{max} tumour-to-background	22.55 ± 2.02 (n = 122)	30.51 ± 1.83 (n = 51)	0.005
SUV_{max} liver-to-background	10.47 ± 1.39 (n = 207)	8.98 ± 1.35 (n = 81)	<0.001
SUV_{max} tumour-to-liver	2.12 ± 1.97 (n = 122)	3.42 ± 1.83 (n = 51)	<0.001

Data are displayed as mean ± SD with number of scans in the parentheses
† Unpaired t-test was used and a p < 0.05 was considered as statistically significant

± 1.35 vs 10.47 ± 1.39; $p < 0.001$). When looked at long acting lanreotide and octreotide separately (Table 3), both SSAs showed a significant decrease in physiological liver SUV_{max} (respectively 9.17 ± 1.35; $p = 0.005$ and 8.54; $p = 0.003$ vs 10.47 ± 1.39).

Effect of SSA treatment on tumour-to-liver ratio

The tumour-to-liver ratio of 173 scans was calculated (122 in the non-treatment group, 51 in the SSA treatment group) (Table 2). Overall, the tumour-to-liver ratio in patients treated with a long-acting SSA prior to the PET/CT scan was significantly increased compared the patients who had not undergone SSA treatment (3.42 ± 1.83 vs 2.12 ± 1.97; $p < 0.001$). Figure 1 shows a visual display of a higher tumour-to-liver ratio after long-acting SSA treatment compared to no SSA treatment. The liver shows a decrease in intensity, making tumour lesions more visible.

The tumour-to-liver ratio was also significantly increased in patients using long acting lanreotide (3.05 ± 1.84 vs 2.12 ± 1.97; $p = 0.005$) and long acting octreotide (4.39 ± 1.68 vs 2.12 ± 1.97; $p < 0.001$) (Table 3).

Effect of SSA treatment on SUV_{max} values in relationship to interval

There were 42 scans where patients had their last SSA treatment 4 weeks prior to the PET/CT scan. Additionally, there were 39 scans where the last SSA administration was between 4 weeks and 3 months (Table 4). There was a statistically significant difference in the SUV_{max} of the primary tumour ($p = 0.029$), SUV_{max} of the liver ($p = 0.001$) and the tumour-to-liver ratio across the three subgroups ($p < 0{,}001$). The SUV_{max} of the primary tumour and the tumour-to-liver ratio in the two groups who had undergone SSA treatment were increased compared to no treatment, whereas the SUV_{max} of the liver was decreased. Furthermore, post hoc testing using Bonferroni correction showed no significant difference of the SUV_{max} tumour ($p = 1{,}000$), SUV_{max} liver ($p = 1{,}000$) and tumour-to-liver ratio ($p = 1{,}000$) between the two groups with SSA treatment (Table S1).

DISCUSSION

This study showed a significant higher uptake of ^{68}Ga-DOTATATE in the primary tumour lesions and significant lower physiological uptake in the liver after treatment with long-acting SSA. This lead to an increased tumour-to-liver ratio. These results are partially consistent with previously conducted studies that were similar to ours, which showcased that treatment with long-acting SSA prior to PET/CT imaging may have no negative effect on ^{68}Ga-DOTATATE uptake.

Haug et al. demonstrated a significant decrease of the average ^{68}Ga-DOTATATE SUV_{max} in the liver (7.1 ± 2.1 vs 9.3 ± 2.9; $p < 0.001$) and spleen (18.4 ± 6.4 vs. 24.9± 6.7, $p < 0.001$) after prior treatment with long-acting octreotide. No significant changes was shown in the uptake in the primary tumour and metastatic lesions *(16)*. Ayati et al. demonstrated a decreased SUV_{max} in the liver (7.6 ± 2.5 vs 9.8 ± 2.3, $p = 0.012$), spleen (18.8 ± 7.3 vs 24.5 ± 8.3; $p = 0.001$) and thyroid (2.6 ± 1.4 vs 3.9 ± 1.4; $p < 0.001$), but no significant changes was shown in the primary tumour or metastatic lesions *(17)*. Cherk et al. showed similar results as Ayati et al *(18)*. Aalbersberg et al. performed a prospective study where ^{68}Ga-DOTATATE PET/CT imaging was performed 1 day before and 1 day after lanreotide treatment and showed comparable results to our study. Where tumour lesion SUV_{max} after lanreotide treatment was significantly increased (21.64 ±

Table 3: Overview of SUV_{max} values between no SSA treatment and long-acting lanreotide or long-acting octreotide treatment

Parameter	No SSA treatment	Lanreotide	Octreotide	*p*†*	*p*††*
SUV_{max} tumour-to-background	22.55 ± 2.02 (n = 122)	28.38 ± 1.89 (n = 35)	35.73 ± 1.66 (n = 16)	0.070	0.003
SUV_{max} liver-to-background	10.47 ± 1.39 (n = 207)	9.17 ± 3.35 (n = 57)	8.54 ± 1.34 (n = 24)	0.005	0.003
SUV_{max} tumour-to-liver	2.12 ± 1.97 (n = 122)	3.05 ± 1.84 (n = 35)	4.39 ± 1.68 n = 16	0.004	<0.001

Data are displayed as mean ± SD with number of scans in the parentheses
† p-value of no SSA treatment compared to long-acting lanreotide treatment
†† p-value of no SSA treatment compared to long-acting octreotide treatment
* Unpaired t-test was used and a p < 0.05 was considered as statistically significant

Table 4: Overview of SUV_{max} values between No SSA treatment, SSA treatment (<4 weeks) and SSA treatment (4 weeks – 3 months)

Parameter	No SSA treatment	SSA treatment (< 4 weeks)	SSA treatment (4 weeks - 3 months)	*p*†
SUV_{max} tumour-to-background	22.55 ± 2.02 (n = 122)	31.01 ± 1.96 (n = 27)	29.95 ± 1.69 (n = 24)	0,029
SUV_{max} liver-to-background	10.47 ± 1.39 (n = 207)	9.27 ± 1.31 (n = 42)	8.67 ± 1.39 (n = 39)	0,001
SUV_{max} tumour-to-liver	2.12 ± 1.97 (n = 122)	3.30 ± 1.89 (n = 27)	3.56 ± 1.78 (n = 24)	<0,001

Data are displayed as mean ± SD with number of scans in the parentheses
† One-way ANOVA was performed and $p < 0.05$ was considered statistically significant

12.63 vs 20.96 ± 12.37; $p = 0.034$) and normal liver uptake was significantly decreased (9.08 ± 2.34 vs 10.15 ± 2.26; $p < 0.001$), resulting in an increased tumour-to-liver ratio (2.59 vs 2.21; $p < 0.001$). However, the increase in tumour SUV_{max} was deemed not clinically relevant *(19)*. In a more recent study, Galne et al. showed no difference in average tumour SUV_{max}, but did show a decrease in normal liver SUV_{max} (6.0 vs 8.6; $p < 0.001$) and an increase in tumour-to-liver ratio (4.3 vs 2.1; $p = 0.01$) after long-acting SSA treatment. Corresponding with our study, Galne et al. also showed no association of SUV_{max} in relationship to interval of long-acting SSA administration before imaging *(20)*.

To our knowledge, our results are the first to retrospectively show a possible clinically relevant increase in ^{68}Ga-DOTATATE tumour lesion uptake. The cause for an increased tumour uptake, but on the contrary decreased liver uptake, is uncertain. In vivo studies have shown that SSRT agonism can lead to internalization of the receptor. A possible explanation for our results could be the difference in receptor internalization and upregulation in normal tissue compared to tumour tissue *(22, 23)*. Continuous SSTR agonism can lead to possible receptor upregulation, which could explain the increase in tumour SUV_{max}. Agonist-induced internalization is most likely to be reversible, which thereafter could lead to potential upregulation of SSTR after SSA treatment *(24)*.

In the first sub-analysis we looked at the effect of long-acting lanreotide and octreotide separately. Both lanreotide as octreotide showed a significant decrease in normal liver uptake, causing a significantly increased tumour-to-liver ratio. When looked at the primary tumour uptake, only octreotide showed a significant increase. Long-acting SSAs are often administered every 4 weeks and reach steady state after approximately 3 injections. Nevertheless, octreotide and lanreotide display a different pharmacokinetic profile *(25)*. This could explain the different effect that was observed between the two long-acting SSAs. However, the sample size of these subgroups were relatively small, so it is uncertain whether there is an actual difference between lanreotide and octreotide in relation to ^{68}Ga-DOTATATE uptake based on these results. It would seem relevant to further research whether there is a variable effect between the two long-acting SSAs on ^{68}Ga-DOTATATE uptake.

The results of this study, alongside previous conducted studies, could have implications for the current guidelines that recommend to discontinue long-acting SSAs 3-4 weeks prior to imaging. Our findings further fuel the question whether these guidelines are still justified, because SSA continuation seems to be favourable for tumour detectability by increasing the tumour-to-liver ratio. Moreover, a lower tumour-to-liver ratio is associated with worse disease progression *(26)*. This increased ratio could also be beneficial for ^{177}Lu-DOTATATE therapy, where it can possibly increase dose delivery to the tumour, while reducing adverse effects by decreasing delivery to normal tissue. However, it is not certain that these results can be directly translated to PRRT, since ^{68}Ga-DOTATATE requires a lower dosage. Thus, more research on the effect of SSA treatment on PRRT is needed to conclude this. In addition, it would seem valuable to continue long-acting SSA treatment, since its effect controls tumour symptoms and delays disease progression.

Due to the heterogenic nature of NET, it is not certain whether these results could be generalized to all types of NET. It is also important to note that there are several other factors that might impact tumour SUV_{max}, like activity, amount of peptide, volume of distribution, tumour size and receptor density *(20)*. This dynamism of ^{68}Ga-DOTATATE uptake could possibly explain why there

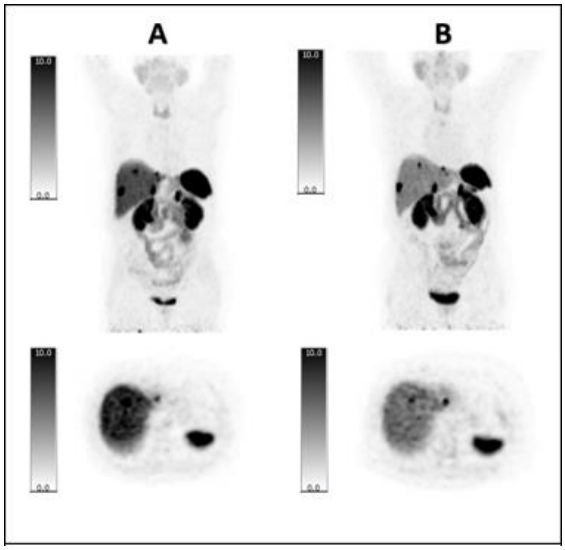

FIGURE 1. Coronal (top) and axial (bottom) ^{68}Ga-DOTATATE PET/CT view of the same patient (A) before long-acting SSA treatment and (B) after long-acting SSA treatment.

was no effect seen when comparing different intervals of SSA administration. However, in this study the tumour-to-background ratio, liver-to-background ratio and tumour-to-liver ratio was used. A tumour-to-normal tissue ratio reduces many factors that can decrease SUV_{max} accuracy *(27)*. Furthermore, it should be mentioned to interpret increased tumour intensity in patients with long-acting SSA therapy with caution. Because increased tumour intensity could be caused by SSA treatment, which could wrongly be seen as disease progression.

There are several limitations to this study that will be addressed. Firstly, the retrospective nature of this study could be seen as a limitation. Secondly, in the period of 2016-2022 two different scanners where used and SUV_{max} has been shown to be variable across different PET/CT scanners *(27)*. To compensate for this, we used the tumour-to-background and liver-to-background ratio. This could have led to inflated SUV_{max} values, which may explain the higher tumour SUV_{max} values compared to previous studies. Moreover, there was a great variety between the last SSA injection (29.33 ± 17.16 days) and the PET/CT scan, which could have influenced the results. Whereas there was a chance of tumour progression or regression occurring in patients who had long intervals. Our sub-analysis however has shown that there was no relationship in SUV_{max} to interval. As there was no difference found in the SUV_{max}-to-background when the last SSA injection was <4 weeks compared to >4 weeks – 3 months (p = 1.000). Additionally, we didn't compare patients intra-individually. This study had a relatively large sample size. Nonetheless, a bigger sample size could have further reinforced our results, but this was not possible due to time limitation. Because of this time limitation, we did not look at the effect of long-acting SSA therapy on ^{68}Ga-DOTATATE uptake in metastatic lesions and other tissues that may show physiological ^{68}Ga-DOTATATE uptake (e.g. spleen, kidneys, adrenal gland), which could have been relevant.

CONCLUSION

Treatment with long-acting SSAs prior to ^{68}Ga-DOTATATE PET/CT imaging did not reduce ^{68}Ga-DOTATATE uptake in the primary tumour lesion. On the contrary, it showed an increase uptake in the primary tumour. Furthermore, treatment with long-acting SSAs lead to a decrease in physiological liver uptake, resulting in an increased tumour-to-liver ratio. These findings further supports the impression that discontinuation of SSA treatment 3-4 weeks prior to imaging is unnecessary, which could have implications for the current guidelines. An increased tumour-to-liver ratio can be beneficial for better tumour lesion detection with ^{68}Ga-DOTATATE PET/CT imaging. Moreover, higher tumour lesion uptake and tumour-to-liver ratio and a lower physiological liver uptake could increase the likelihood of patients being suitable for PRRT and may enable higher dosage of PRRT reaching the tumour, while decreasing normal tissue damage.

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SUPPLEMENTARY

Table S1: Bonferroni Post Hoc test. Comparison between no SSA treatment, SSA treatment <4 weeks and SSA treatment 4 weeks – 3 months

Variable	Groups		Mean difference	SD	*p*†
SUV_{max} tumour-to-background	No SSA	SSA (<4 weeks)	0.73	1.15	0.084
		SSA (>4 weeks)	0.75	1.16	0.186
	SSA (<4 weeks)	No SSA	1.38	1.15	0.084
		SSA (>4 weeks)	1.04	1.21	1.000
	SSA (>4 weeks)	No SSA	1.33	1.16	0.186
		SSA (<4 weeks)	0.97	1.21	1.000
SUV_{max} liver-to-background	No SSA	SSA (<4 weeks)	1.13	1.06	0.079
		SSA (>4 weeks)	1.21	1.06	0.003
	SSA (<4 weeks)	No SSA	0.89	1.06	0.079
		SSA (>4 weeks)	1.07	1.07	1.000
	SSA (>4 weeks)	No SSA	0.83	1.06	0.003
		SSA (<4 weeks)	0.94	1.07	1.000
SUV_{max} tumour-to-liver	No SSA	SSA (<4 weeks)	0.64	1.15	0.006
		SSA (>4 weeks)	0.59	1.16	0.002
	SSA (<4 weeks)	No SSA	1.56	1.15	0.006
		SSA (>4 weeks)	0.92	1.20	1.000
	SSA (>4 weeks)	No SSA	1.68	1.16	0.002
		SSA (<4 weeks)	1.08	1.20	1.000

†$p < 0.05$ was considered statistically significant