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ORIGINAL ARTICLE

Does Treatment with Somatostatin Analogs Affect the Radioactivite Uptake of Normal Target Organs and Malignant Lesions on ^{68}Ga-DOTATATE PET/CT imaging?

Somatostatin Analogları ile Tedavi, ^{68}Ga-DOTATATE PET/BT Görüntülemede Normal Hedef Organların ve Malign Lezyonların Radyoaktivite Alımını Etkiler mi?

[1]Farise Yılmaz, [1]Hasan Önner, [1]Gonca Kara Gedik, [2]Özlem Şahin, [1]Ahmet Volkan Çelik, [2]Çağlagül Erol

[1]Selcuk University Medical Faculty, Department of Nuclear Medicine, Konya
[2]Necmettin Erbakan University Meram Medical Faculty, Department of Nuclear Medicine, Konya

Correspondence

Farise Yılmaz, Associate Professor of Nuclear Medicine, Selcuk University Medical Faculty, Department of Nuclear Medicine, Konya/TURKEY

E-Mail: drfarise@hotmail.com

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ABSTRACT

Objective: Somatostatin analogs (SSA) are used in treating low-grade neuroendocrine tumors (NET), mainly because of their antiproliferative effect. 68Ga tetraazacyclododecantetraacetic acid-DPhe1-Tyr3-octreotate (DOTATATE) PET/CT as somatostatin receptor imaging has been widely used in recent years. However, there are conflicting publications in the literature, although there are guidelines for discontinuing the use of SSA before imaging. This study aims to investigate the effect of SSAs on Somatostatin receptor imaging.
Material and Method: We retrospectively analyzed 253 patients who underwent 68Ga-DOTATATE PET/CT imaging between 2018 and 2022. Among these patients, those with low grades (grade 1 and grade 2) using SSA were included in the study. SUVmax (maximum standard uptake volume) of normal target organs, primary tumors, and metastases with the highest SUVmax in each organ were compared before and after SSA treatment.
Results: 28 patients (16 females; 12 males, age [mean±SD], 54.82±14.27, range 18-78) with low-grade NET and ^{68}Ga-DOTATATE PET/CT imaging with SSA therapy were included in the study. Although SUVmax was decreased in the values measured after SSA application in the liver and spleen, it was not statistically significant (p>0.05). There was no significant difference between SUVmax values in primary tumors and metastatic lesions in the liver, bone, lung, or lymph nodes before and after SSA application (P> 0.05).
Conclusion: In conclusion, these drugs do not need to be discontinued before 68Ga-DOTATATE PET/CT imaging for treatment follow-up in neuroendocrine tumor patients using SSAs. In addition, these drugs may help report interpretation by increasing the intensity of metastatic lesions in the liver and spleen.

Keywords: ^{68}Ga-DOTATATE PET/CT, Somatostatin analogs, Neuroendocrine tumors.

ÖZ

Amaç: Somatostatin analogları (SSA), esas olarak antiproliferatif etkileri nedeniyle düşük dereceli nöroendokrin tümörlerin (NET) tedavisinde kullanılır. 68Ga-tetraazasiklododekantetraasetik asit-DPhe1-Tyr3-oktreotat (DOTATATE) PET/BT somatostatin reseptör görüntüleme son yıllarda yaygın olarak kullanılmaktadır. Bununla birlikte, görüntülemeden önce SSA kullanımının kesilmesine yönelik kılavuzlar olmasına rağmen, literatürde çelişkili yayınlar bulunmaktadır. Bu çalışma, SSA'ların somatostatin reseptör görüntülemesi üzerindeki etkisini araştırmayı amaçlamaktadır.
Gereç ve Yöntem: 2018-2022 yılları arasında ^{68}Ga-DOTATATE PET/BT görüntülemesi yapılan 253 hastayı geriye dönük olarak inceledik. Bu hastalardan SSA kullanan düşük dereceli (grade 1 ve grade 2) olanlar çalışmaya dahil edildi. Normal hedef organların, primer tümörlerin ve her organda en yüksek SUVmax'ı (maksimum standart alım hacmi) olan metastazların değerleri SSA tedavisinden önce ve sonra karşılaştırıldı.
Bulgular: SSA tedavisi ile düşük dereceli NET ve 68Ga-DOTATATE PET/BT görüntülemesi olan 28 hasta (16 kadın; 12 erkek, yaş [ortalama±SD], 54.82±14.27, aralık 18-78) çalışmaya dahil edilmiştir. Karaciğer ve dalakta SSA uygulaması sonrası ölçülen değerler, SUVmax azalmasına rağmen istatistiksel olarak anlamlı değildi (p>0.05). Primer tümördeki SUVmax değerleri ile karaciğer, kemik, akciğer veya lenf nodlarındaki metastatik lezyonlarda SSA uygulaması öncesi ve sonrası arasında anlamlı fark bulunmadı (P> 0.05).
Sonuç: SSA kullanan nöroendokrin tümörlü hastalarda tedavi takibi için 68Ga-DOTATATE PET/BT görüntülemeden önce kesilmeyebilir. Ayrıca SSA kullanımı karaciğer ve dalaktaki metastatik lezyonların görünürlüğünü artırarak raporun yorumlanmasına yardımcı olabilir.

Anahtar Kelimeler: ^{68}Ga-DOTATATE PET/BT, Somatostatin analogları, Nöroendokrin tümörler.

Introduction

^{68}Ga-DOTATATE PET/CT has taken an important place in the treatment management of neuroendocrine tumors (NET) in recent years (1). Compared with conventional imaging methods (In111; Octreoscan), PET/CT imaging for NETs has become increasingly prominent with better sensitivity and specificity, low radiation dose, and easy production possibilities (2, 3). Primary tumor localization, staging, and response to treatment are among the indications. It has also played an important role in predicting response to treatment.

Synthetic somatostatin analogs (SSA) are clinically effective by prolonging the progression time and controlling symptoms in patients with active and low-grade NET, with an antiproliferative effect (4, 5). However, there are also guidelines that SSAs mask tumor detection because they are saturated with their

somatostatin receptors (SSTRs) in malignant lesions (1, 6-8). Reports have also shown upregulation of SSTR expression and changes in the internalization of subtype 2 SSTRs in tumor cells after initiation of somatostatin analog therapy (6, 7). These observations may be due to the complex mechanism of the effect of octreotide on tumoral lesions. Clinical studies on this subject mainly evaluated the effect of octreotide treatment on Octreoscan imaging (9). In recent years, several articles have investigated the effect of octreotide on PET/CT and SSTR imaging(10, 11). This study aimed to evaluate whether 68Ga-DOTATATE expression differs in primary NETs, metastases, and some target organs before and after treatment with somatostatin analogs.

Material and Method

253 patients who underwent ^{68}Ga-DOTATATE PET/CT imaging at the institutions were determined retrospectively. Among these patients, 28 patients diagnosed with grade 1 and grade 2 low-grade NET and treated with SSA were included in the study. Patients managed with active surveillance for GEP-NET, surgery, PRRT (peptide receptor radionuclide therapy), liver-directed therapy, or other systemic anti-tumor therapy, and patients with active secondary malignancies, including NET; pregnancy, lactation, and those under 18 years of age are excluded. 28 patients (16 females; 12 males, age [mean±SD], 54.82 ±14.27, range 18-78) with grade 1 and 2 NET and 68Ga-DOTATATE PET/CT imaging before and after SSA treatment were included in the study. 68 Ga-DOTATATE PET/CT images were made by nuclear medicine physicians with at least five years of experience. Before the study, approval was obtained from the Ethics Committee of Selcuk University Faculty of Medicine (2022/329).

Demographic characteristics of patients, tumor grade, organ of origin of the tumor, whether or not they were operated on, SSA reports (lanreotide or octreotide), the time between SSA treatment and last imaging, and doses were obtained from the hospital information system (Enlil), from https://enabiz.gov.tr/ and from the anamnesis forms of the patients. If the patient had multiple imaging before and after SSA application, the last scan before treatment and the first or second scan after treatment were selected. SUVmax was calculated from the primary lesion (if any) and from the metastasis with the highest SUV in each organ. DOTATATE uptake was assessed using regions of interest (ROI) plotted to encompass the entire organ for the pituitary gland and adrenal glands. A circular 2 cm ROI was drawn for liver, spleen, primary lesion, and metastases. SUVmax was calculated using the maximum concentration in the ROI, patient body weight, and injected dose [SUVmax = maximum activity concentration/(injected dose/body weight)].

^{68}Ga-DOTATATE PET/CT imaging

^{68}Ga- DOTATATE was prepared in a fully automated system (Scintomics GRP synthesis module, Germany) within the department. It was scanned with a hybrid PET/CT scanner (Biograph mCT, Siemens, Germany) in the Department of Nuclear Medicine 45-60 minutes after the intravenous injection of 110-185 MBq of 68Ga-DOTATATE. Whole body images were obtained from the base of the skull to the middle of the thigh in 8 or 9-bed positions, with an acquisition time of 2 minutes per bed. Low-dose 16-slice multidetector CT scanning (acquisition parameters: 190 mA, 140 kV, and section width 5.0 mm) was used. A standard whole-body PET scan was performed in 3D mode. CT-based attenuation correction of emission images was used. After completion of PET acquisition, reconstructed attenuation corrected PET images, CT images, and fused images of matching PET and CT image pairs were examined in three-dimensional cine mode in the axial, coronal, and sagittal planes and maximum intensity projections.

Statistical Analysis

All statistical analyses were performed using *R* version 3.6.0 (The *R* Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). To check the normality of the data, Shapiro-Wilk's normality test and Q-Q plots were used. Numerical variables were expressed as mean ± standard deviation, median with range (minimum-maximum), or median with interquartile (25th percentile – 75th percentile), as appropriate. Categorical variables were also described as count (*n*) and percentage (%). A Paired sample *t*-test or Wilcoxon test was run to determine whether there was a statistically significant difference between the initial and last measurement of the parameters. A *p*-value less than 5% was considered statistically significant.

Results

Two hundred and fifty-three patients who underwent ^{68}Ga-DOTATATE PET/CT imaging were reviewed retrospectively. Among these patients, 228 patients with pathological diagnoses of NET were found.

One hundred and thirty-two patients had gastroenteropancreatic, 54 respiratory system, 16 liver, and 26 other NET diagnoses. It was determined that 37 patients (grade 1 and 2 patients) with low-grade NET were given SSA treatment. However, 2 of these patients were excluded from the study because they started short-term SSA treatment and then a chemotherapy regimen, and 7 of them had only one imaging. Twenty-eight patients were included in the study. Of 28 patients, 16 were female, and 12 were male, with a mean age of 54.82 (range 18-78). Nineteen of these patients were grade1 (68%) and 9 GR2 (32%). These patients were diagnosed with 1 cecum, 1 thymus, 6 small intestines, 8 pancreases, 1 liver, 1 omentum, 1 over, 1 paraganglioma, 6 lungs, and 2 other. There were lymph nodes (n:13 /% 46.4), bones (n:2 /%14.3), and liver metastases (n:11 /%39.3). The median follow-up time was 10 months (range: 3 – 36 months). 60 mg

of lanreotide (Somatuline autogel) was given to one patient, 30 mg of lanreotide (Somatuline autogel) to 13 patients, and 30 mg of octreotide (Sandostatin LAR) to 14 patients. The time between scans was 7.5 (3-36) months. The time between SSA injection and first imaging was 28.2 (1-32) days. The demographical and clinical characteristics of the patients were given in Table 1. In our study, 78.6 % (22/28) had stable or partial regression, and 21.4 % (6/28) had progressive disease. There was no statistically significant difference in SUVmax values in primary lesions (before, median (IQR):28.98 ; after, median (IQR):23.51, p=0.464) and metastases (liver: before, median (IQR):37.60; after, median (IQR):35.62, p>.999, lymph node: before, median (IQR):23.04; after, median (IQR):31.02, p=0.946, bone: before, median (IQR):14.79; after, median (IQR):13.16, p=0.250) before and after treatment.

In addition, although the target normal organs, liver and spleen, decreased in percentage before and after treatment, no statistically significant difference was found (respectively p=0.624, p=0.113). There was no significant difference in the pituitary gland and right-left adrenal glands (respectively p=0.572, p=0.650, p=0.105). The comparison of the before and last measurement of the parameters is given in Table 2. Figure 1 shows ^{68}Ga-DOTATATE PET/CT images from a patient before and after SSA treatment.

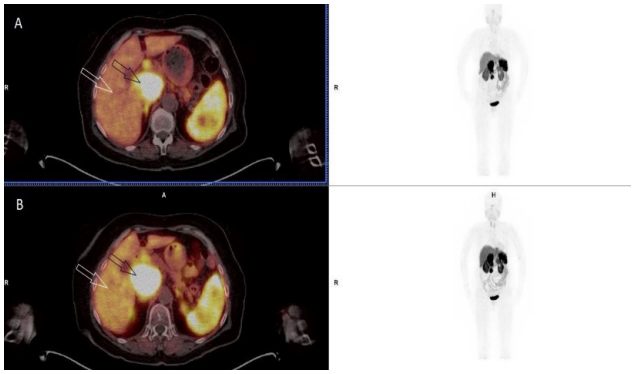

Figure 1. A 75-year-old female patient diagnosed with a pancreatic neuroendocrine tumor, 30 mg of lanreotide (Somatuline autogel/4 weeks) for 18 months before (A) and after (B) 68Ga-DOTATATE PET/CT whole-body maximum-intensity projection (MIP) images. The lesion in the pancreas (black arrow) shows similar uptake in the pre-treatment (SUVmax: 39.10) and post-treatment (SUVmax: 42.26) images. A slight decrease is noted in the liver (white arrow). It is similar in other normal target organs.

Table 1. Demographical and clinical characteristics of the patients

	Patients (*n*=28)
Demographical characteristics	
Age (years), mean ± SD (min-max)	54.82 ± 14.27 (18 – 78)
Gender (F/M), *n* (%)	16 (57.1) / 12 (42.9)
Clinical characteristics	
Ki-67 levels (Grade 1/Grade 2), *n* (%)	19 (67.8) / 9 (32.2)
Surgery, *n* (%)	16 (57.1)
SSA (L/O), *n* (%)	14 (50) / 14 (50)
^{68}Ga DOTATATE imaging interval (months), median (min-max)	7.5 (3 – 36)
SSA injection-first imaging (days), median (min-max)	28.2 (1-32)

SSA: Somatostatin analogs L: lanreotide O: Octreotide

Table 2. SUVmax comparison of the normal target organ and malignant lesions before and after

	Initial	**Last**	***p*-value**
N. liver SUVmax, median (IQR)	11.41 (9.63 – 13.80)	10.02 (9.02 – 13.78)	.624[1]
N. spleen SUVmax, mean ± SD	31.34 ± 10.07	25.68 ± 7.01	.113[2]
Pituitary SUVmax, mean ± SD	8.78 ± 3.78	9.03 ± 3.51	.572[2]
Right adrenal in, mean ± SD	20.47 ± 9.41	19.89 ± 9.10	.650[2]
Left adrenal in, mean ± SD	18.02 ± 7.77	20.07 ± 8.66	.105[2]
Primary lesion in, median (IQR)	28.98 (12.49 – 42.30)	23.51 (19.16 – 44.73)	.464[1]
Liver met in, median (IQR)	37.60 (32.87 – 53.87)	35.62 (29.50 – 50.61)	>.999[1]
LN met in, median (IQR)	23.04 (16.03 – 42.55)	31.02 (18.90 – 40.80)	.946[1]
Bone met in, median (IQR)	14.79 (10.94 – 18.83)	13.16 (9.14 – 16.66)	.250[1]

1 Wilcoxon test
2 Paired sample *t*-test
p<.05 was considered statistically significant.
N: Normal, met: metastasis,

Discussion

SSTR imaging guidelines recommend discontinuing octreotide therapy before imaging, as SSTRs in tumor cells may interact and compete with the radiolabelled peptide. However, in various studies (in vivo or in vitro), it has been suggested that there is a large increase in agonist internalization and different levels of expression at the receptor level, especially in SSTR2, after cold octreotide treatment (7, 12, 13).

In our study, we found that primary tumors and metastatic lesions showed similar uptake of ^{68}Ga-DOTATATE PET/CT after administration of the somatostatin analog, while there was a slight decrease in normal liver and spleen, although not statistically significant. Galne et al. in a prospective study with more participants, found no difference in ^{68}Ga- DOTATATE uptake in tumors, as in our study, but found a decrease in normal liver uptake. Therefore, they found an increase in the tumor/liver ratio. They suggested that this would affect the interpretation and that the recommendation for discontinuation of SSA drugs in the guidelines should be re-evaluated. They also showed that the time between the last SSA injection and imaging was not significant in tumor or liver SUVmax (14). Ayati et al., including 30 patients, showed a decrease in liver, spleen, and thyroid uptake before and after treatment with long-acting SSA, and with ^{68}Ga-DOTATATE PET/CT, but they did not find any significant difference in primary tumor and metastatic lesions. Similarly, they claimed that there is no need to discontinue SSA drugs before 68GA-DOTATATE imaging and that an increase in the tumor/background ratio will facilitate interpretation (15). They attributed this difference to different patterns of internalization in normal tissue and tumor cells, and possibly to reduced uptake in tumors by their compensatory mechanisms. Again, in a study conducted in previous years, two groups were formed, ^{68}Ga-DOTATATE PET/CT scans before and after octreotide treatment did not find a significant difference in malignant lesions, but they found a decrease in the liver and spleen (16). It may also be due to the upregulation of receptors after treatment with SSA. These heterogeneous behavioral patterns in SSRTs perhaps preclude the expected reduction in ^{68}Ga-DOTATATE expression in malignant lesions treated with SSA after interaction (17). Cherk et al., in a retrospective study with 21 patients with a similar purpose, found a decrease in ^{68}Ga-DOTATATE uptake in the liver, spleen, and thyroid gland, a slight increase in the pituitary gland, and no significant difference in the adrenal glands and salivary glands. Thus, they found the rate of metastatic lesion/liver uptake to be high as in other studies. They claimed that knowing this situation would prevent the better selection of tumor tissue from mistakenly evaluating it as progression. In addition, the author emphasized that the administration of SSA treatment before PRRT and the high tumor/spleen-liver ratio will both reduce the amount of radiation that may cause myelosuppression in the spleen, and increase the effectiveness of the treatment by giving more intense doses in tumoral tissues (18).

As in other rare studies in the literature, we have shown that treatment with SSA does not pose a significant disadvantage in staging the disease and detecting metastases. However, although we could not detect a statistically significant decrease in liver and spleen, we saw a decrease in visual and percentage. This may be because it was a retrospective study, the number of patients included in the study was relatively small, and the time between SSA injection and imaging could not be standardized. It also depends on the activity and amount of peptide injected, the injection time, the resolution of the detector system, the size of the low-resolution.

To reduce the adverse effects of SSA therapy, some guidelines recommend scheduling imaging for a 28-day period, just before the next dose. However, in another study, they found that long-acting octreotide showed a steady-state profile with a longer maintenance period of more than 0.01 ng/mL/mg at 12-13 weeks (19). In our study, this period was 28.2 days. More studies comparing ^{68}Ga-DOTATATE with patients with a time interval of less than or more than 28 days between the last SSA injection and imaging are required.

A small number of patient studies with 111In-DTPA, one of the traditional SSRT imaging studies, found a significant reduction in tracer uptake in some organs (liver, spleen, and kidney), but an increase in tumor lesions after lanreotide treatment. SSRT imaging with 111In-DTPA causes imaging due to the use of slower pharmacokinetic agents, limited dose administration to the patient (1-2 mCi), and high-energy gamma emissions (9, 20).

The limited number of patients in our study, being retrospective, and the long interval between two imaging can be counted among our limitations. We think that prospective studies in which the imaging time is planned to be shorter with SSA injection will further illuminate this issue.

In conclusion, in neuroendocrine tumor patients using somatostatin analogues, these drugs may not need to be discontinued prior to ^{68}Ga-DOTATATE PET/CT imaging for treatment follow-up. Moreover, continued use of these drugs may contribute to interpretation by increasing tumor intensty in the liver.

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