Is SUVmax a useful marker for progression-free survival in patients with metastatic GEP-NET receiving ^{177}Lu-DOTATATE therapy?

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Abstract

Objective: The prognostic potential of pretreatment maximum standardized uptake volume (SUVmax) on gallium-68-DOTATATE was evaluated with positron emission tomography/computed tomography (^{68}Ga-DOTATATE PET/CT) in 37 patients with G1/G2 gastroenteropancreatic neuroendocrine tumors (NET) who received peptide receptor radionuclide therapy (PRRT) with lutetium-177-[DOTA°,Tyr3] octreotate (^{177}Lu-DOTATATE) after the failure of somatostatin analogues. **Methods:** The mean and total SUVmax were used in ^{68}Ga-DOTATATE PET/CT before ^{177}Lu-DOTATATE treatment to assess the progression-free survival (PFS). **Results:** The responses of the patients were evaluated as partial response in 8 (32%) patients, stable disease in 12 (48%), and progressive disease in 5 (20%). The median PFS was 18 months; longer than this threshold in 14 patients (26.0 months) and shorter in 11 (8.4 months). The mean SUVmax of metastases in the liver (34.15±17.89 vs. 14.69±9.17, P=0.004) and mean SUVmax of all body metastatic lesions (33.05±14.32 vs. 15.26±4.84, P=0.001) were higher in patients with longer PFS. The tumor grade, the origin of the tumor, Ki67 status, and previous somatostatin treatment history were not significantly different between the two PFS groups. **Conclusions:** The pre-treatment SUVmax values of ^{68}Ga-DOTATE PET/CT in lesions are a potential prognostic factor for PFS in well-differentiated gastroenteropancreatic neuroendocrine tumors undergoing ^{177}Lu-DOTATATE treatment and could be a useful parameter for the treatment selection.

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Introduction

Epithelial neuroendocrine neoplasms (NEN), which are rare and arise from neural crest cells throughout the body, are particularly well-described in gastroenteropancreatic and bronchopulmonary tissues. Although gastroenteropancreatic neuroendocrine tumors (GEP-NET) are less common than other solid tumors, their incidence has increased 3-5 times over the past few decades [1-5]. In addition, differences in genetic and biological behaviors, functional status, variations in pathological features between primary tumor and metastases, and somatostatin receptor variants contribute to heterogeneity [6-8].

While surgical resection is the only therapeutic approach at the local stage, treatment of NET in metastatic disease is difficult. There is limited consensus regarding the treatment of metastatic GEP-NET due to the scarcity of randomized prospective studies and low cure rates [9-11]. Current guidelines support the use of somatostatin analogs (SSA) to control the hypersecretion of hormonal neuropeptides in functional tumors and prevent tumor proliferation [12]. Other therapies, such as chemotherapy, tyrosine kinase inhibitors (sunitiniband pazopanib), and everolimus are preferred to achieve a stable disease status rather than partial regression in well-differentiated NET [13-16]. Peptide receptor radionuclide therapy (PRRT) using radiolabeled SSA was approved in Europe and the United States in 2017 and 2018, respectively, as a new treatment option in somatostatin expressing (SSTR) GEP-NET patients [17]. Peptide receptor radionuclide therapy significantly improves survival and quality of life with 15%-35% response rates reported in unresectable and metastatic GEP-NET patients [18]. However, the disease eventually progresses, and therapy options remain limited thereafter.

A reliable method with better clinical efficacy is needed to be able to assess the treatment response of PRRT in NET. In addition to conventional radiology, molecular imaging contributes to diagnosis, staging and re-staging following treatment [19, 20]. It is unclear why some GEP-NET patients respond well to Lutetium-177-[DOTA°,Tyr3]octreotate (^{177}Lu-DOTATATE) and others do not. Standardized uptake value (SUV) is the mainstay

semi-quantitative measurement utilized in PET imaging, which provides qualitative visual data as well as quantitative measures to evaluate tumoral radiopharmaceutical retention and the tumor to background activity ratio. Translational investigation has indicated a connection between somatostatin receptor immunostaining and ^{68}Ga-DOTATATE PET/CT in NET. This imaging methodology depicts the somatostatin receptor status of GEP-NET and demonstrates cell proliferation [21, 22]. However, predictive markers to determine individual PRRT responses remain a critical unmet need. Some biomarkers such as chromogranin A, NETest and alkaline phosphatase are potential indicators of disease status although results are contradictory [23-26].

The impact of conventional PET parameters (SUVmean/max) has been investigated for the estimation of clinical results after PRRT. Standardize uptake value refers to the ratio of the concentration of radiopharmaceutical in a volume of tissue in microcuries of injected agent per volume to concentration in the body if uniformly distributed. Maximum SUV is the highest SUV in pixels located in the region-of-interest (ROI) and mean SUVmax is the average value of SUVmax of each organ. Since SUV accumulation in NET is a semi-quantitative evaluation, the results are contradictory. Werner et al. (2019) stated that intratumoral heterogeneity is superior to SUVmax/mean for the prognosis of pNET before PRRT [27]. Estimating treatment response is fundamental for controlling treatment and to strategically avoid symptoms and costs arising from ineffective medicines. The aim of this study was to evaluate the potential prognostic utility of pretreatment SUVmax on ^{68}Ga-DOTATATE PET for the clinical outcomes of GEP-NET patients who underwent PRRT.

Methods

Subject demographics

From the patients who received ^{177}Lu-DOTATATE in our center from August 2016 to October 2019, the data were retrospectively collected of those with G1 or G2 GEP-NET. Two additional inclusion criteria were adequate tumor somatostatin receptor expression on ^{68}Ga-DOTATATE PET/CT (grade 2 or higher) and a minimum of 6 months clinical follow-up. Patients with previous PRRT, unknown primary tumor site or G3 GEP-NET were excluded from the study. All patients underwent routine physical examinations, laboratory tests, and radiological examinations with CT or magnetic resonance imaging (MRI) to evaluate the location of the tumor before treatment initiation. Previous treatments before PRRT were recorded. The study protocol was approved by the local Ethics Committee of Gaziantep University and all procedures were performed according to the Declaration of Helsinki. Informed consent was obtained from each patient before treatment after a full explanation of the purpose and nature of all procedures used.

Pre-therapeutic PET imaging and assessment

Gallium-68-DOTATATE doses were prepared using an automated synthesis unit, and the images were obtained approximately 60min after intravenous injection of a 100MBq/kg dose. In all cases, long-lasting somatostatin analogs were discontinued a month before imaging. Positron emission tomography scans were obtained in the supine position using a GE Discovery PET/CT scanner (General Electric, Milwaukee, WI, USA). Computed tomograhpy images were acquired from an integrated PET/ CT scanner with the utilization of a standardized convention that included 140kV and 70mA, a cylinder turn time of 0.5s per revolution, a pitch of 6, and an area thickness of 5mm. Positron emission tomography images were acquired for "4min for each bed position,"and were reproduced utilizing CT data for constriction. The PET/CT images were evaluated visually and semi-quantitatively using SUVmax (Maximum Standardized Uptake Value) PET/ CT evaluation criteria by 2 nuclear medicine experts with a minimum of 10 years of PET/CT and 5 years of DOTATATE PET/CT experience. Lesions other than physiological involvement areas were considered positive.

The SUV values of the reference lesion were examined. Standardized uptake value is not expressed in units, but refers to the ratio of the concentration of radiopharmaceutical in a volume of tissue in microcuries of injected agent per volume to concentration in the body if uniformly distributed. The most prominent SUV lesion uptake was selected for the analysis. Standardize uptake value max represents the highest SUV in pixels located in the ROI in the primary tumor, the liver, and other metastases (lung, lymph nodes, bone and peritoneum). In patients with multiple organ metastases, the total SUVmax was obtained by measuring and totalling the SUVmax of each metastasis. The arithmetic mean SUVmax value was calculated by dividing the total SUVmax value by the number of lesions.

^{177}Lu-DOTATATE administration

The same automated synthesis system was used to synthesize the ^{177}Lu-DOTATATE doses. A fixed dose of 7400MBq was administered to all patients in each cycle. Treatment was started at a maximum of one week after pre-therapeutic PET imaging. Patients were treated with a minimum of four cycles of ^{177}Lu-DOTATATE, amounting to a cumulative intended dose of 7400x4:29.6GBq. All patients received 2L of normal saline infusion over 4h, beginning 60min before treatment. Kidney function was observed for 24h. Treatment cycles were repeated every 6 weeks. Planar and single-photon emission computed tomography images were acquired at the 24thhr of treatment.

Post-therapeutic evaluation

The response to treatment with ^{68}Ga-DOTATATE PET/CT was evaluated within three months after the last cycle. Contrast-enhanced CT scans were performed to permit morphological evaluation. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were used to assess the results by comparing the CT sections of PET images.

The option of prolonging the treatment was offered to patients with a persistent, higher tumor burden, who had demonstrated a symptomatic or objective response after

induction to ^{177}Lu-DOTATATE cycles. For patients receiving additional therapy, the treatment was discontinued in cases with tumor progression or persistent toxicity.

The imaging, functional (^{68}Ga-DOTATATE PET/CT) and morphological (CT/MRI) and adverse effect assessments were performed every 3-6 months post-PRRT. Liver and kidney function tests and hemogram were performed at the beginning and during the follow-up period and control visits post-treatment. Side-effects were graded according to the Common Terminology Criteria for Adverse Events v4.0.

Statistical methods

Progression-free survival (PFS) was defined as the period between the first administration of ^{177}Lu-DOTATATE and the time of disease progression or death. Progression-free survival was estimated with the Kaplan-Meier technique using the log-rank test, and the predictive risk factors for progression were analyzed using the univariate Cox proportional hazard method. A value of $P<0.05$ was considered statistically significant. Hazard ratios were presented with 95% confidence intervals. SPSS version 22.0 software was used to evaluate the potential role of SUVmax in prognosis. Patients were stratified according to disease status (progressive disease - stable disease) at a selected follow-up time point

Results

Clinical features of GEP-NET patients

A total of 37 patients underwent PRRT for advanced GEP-NET. Of these 37 subjects, 12 had no comparable ^{68}Ga-DOTATATE PET/CT imaging at 3 months post-PRRT. Of the patients with no PET follow-up, four had only one cycle of treatment and died from early disease progression. Of the eight patients who were followed up during induction, five received two cycles, two received three cycles, and one received four cycles; they had no post-treatment PET scans.

All patients had histologically proven, progressive unresectable or metastatic GEP-NET: 11 had pancreatic cancer and 14 had cancer of other origins (6 gastric, 5 colorectal, and 3 of the small intestine). Twenty two of 25 had metastasis. The liver was the most common site of metastasis (21/22, 95%), followed by bone (13/22, 59%), lymph nodes (12/22, 54.5%) and omentum 5/22, (22%). One-fifth of the patients had surgery before GEP-NET. A total of 22 patients with detailed information on grade with Ki-67, 32% (7/22) were G1 and 68% (15/22) were G2. The previous treatments of the patients were as follows: somatostatin analogs (18/25, 72%), sunitinib (5/25, 20%), chemotherapy (5/25, 20%), everolimus (4/25, 16%) and no treatment (3/25, 12%) (Table 1).

Statistical analysis results

The 25 patients who could be evaluated (14/25 females [56%]; 29-81 years of age) received a total of 147 cycles of lutetium therapy (3-6 cycles to 20 patients, ≥7 cycles to 5 patients). The follow-up period after PRRT ranged from 144 to 1111 days (mean 571 days). During the follow-up period, nine patients died. The median PFS in the GEP-NET patients was 18 months.

According to the reference standard, 8 (32%) patients had a partial response, including one patient with almost complete response. In this patient, multiple small liver metastases and lymph node metastases of a pancreatic NET completely disappeared, and only a few lesions remained in the pancreas and bone. Stable disease was determined in 12 (48%) patients and progressive disease in 5 (20%).

An apparent radiological progression in 2 cases in the early CT evaluation after the second dose manifested as increased lesion diameter. Nevertheless, owing to significant clinical improvement, it was decided to complete the treatment. Both cases showed a stable disease (less than 30% decreases from baseline in target lesions) in ^{68}Ga-DOTATATE PET/CT after completion of ^{177}Lu-DOTATATE therapy.

Quantitative evaluation of ^{68}Ga-DOTATATE

In the current study cohort, PFS varied considerably (4.3-37 months), so the patients were separated into sub-groups to evaluate the potential role of SUVmax on prognosis based on PFS. A PFS of 18 months was chosen as the best cutoff point to distinguish between patients with a good or an inadequate response to PRRT (i.e., patients with prolonged or short PFS). During follow-up, 14 patients had PFS longer than 18 months (26.0 months) and 11 patients had PFS shorter than 18 months (8.4 months). Liver SUVmax was significantly higher in the longer PFS group (34.1) than in the shorter PFS group (14.6) ($P=0.004$). The mean SUVmax of all lesions was determined to be significantly higher in the longer PFS group, independently from progression status (33.1 vs. 15.2, $P=0.001$) (Table 2).

Although the pretreatment mean SUVmax scores of all lesions were significantly higher in patients with stable/partial regressive disease than in those with progressive disease (Table 3), there was no statistically significant difference in total SUVmax, liver SUVmax, and primary SUVmax ($P>0.05$). As indicated by the Cox proportional hazards model, neither the pretreatment mean SUVmax nor the rate of change in SUV was predictive for PRRT response in the univariate analysis. Likewise, the SUVmax values showed no difference according to grade, Ki67 status, and tumor origin (Table 4).

No life-threatening or debilitating side-effects were observed during follow-up. None of the patients had severe nephrotoxicity (grade 3/4). Only 1 patient (4%) had G3 anemia and 2 (8%) patients developed G3 leukopenia and thrombocytopenia and 1 (4%) patient had G4 leukopenia and thrombocytopenia (Table 5).

Discussion

Despite growing treatment options, there has been no significant increase in long-term NET patient survival. Evaluating the adequacy of GEP-NET response to treatment is similarly challenging. Due to their heterogeneous nature, NET may show different SSTR-avid values. The possible related factors affecting long-term PFS were evaluated in this study, and it

Table 1. *Patient characteristics.*

Case	Age	Sex	Primary tumour	Ki67	Gr	Metastases	Previous therapy
1	62	M	Gastric	NA	NA	Liver/bone	Surgery
2	70	M	Gastric	NA	NA	Liver/bone	SSA
3	54	F	Gastric	NA	NA	Liver/LN/bone	SSA
4	66	M	Pancreas	1	1	Liver/bone	SSA, sunitinib, CTx
5	45	M	S. intestine	1	1	Liver/LN/bone	SSA, sunitinib, everolimus
6	40	F	Colorectal	1	1	Liver/LN/bone/omentum	SSA, surgery
7	34	M	Gastric	1	1	Liver	SSA
8	51	M	Pancreas	1	1	Unresectable	SSA, sunitinib
9	55	F	Gastric	1	1	Unresectable	SSA
10	49	F	Pancreas	2	1	Liver/LN/bone	None
11	69	F	Gastric	3	2	Liver/LN/bone/omentum	None
12	75	F	Pancreas	4	2	Liver/LN/bone/omentum	SSA
13	58	M	Pancreas	5	2	Unresectable	SSA
14	55	F	Colorectal	10	2	Liver	SSA
15	68	F	S. intestine	10	2	Liver	SSA, CTx
16	71	f	Colorectal	10	2	Liver	SSA
17	43	f	Pancreas	10	2	Liver/LN/bone	SSA, sunitinib, everolimus
18	36	f	S. intestine	13	2	Liver/bone/omentum	Everolimus, CTx
19	70	m	Pancreas	15	2	Liver/LN	SSA, CTx
20	48	m	Colorectal	15	2	Liver/LN	SSA, CTx
21	48	f	Pancreas	15	2	Liver	None
22	29	m	Pancreas	15	2	Liver/LN	SSA, surgery
23	70	f	Pancreas	20	2	Liver/bone/LN	Surgery
24	78	f	Colorectal	20	2	Bone/omentum	Surgery
25	51	m	Pancreas	20	2	Liver/LN/bone	SSA, sunitinib, everolimus

SSA, somatostatin analog; NA, not available; CTx, chemotherapy; LN, lymph node; Gr, grade; S. intestine, small intestine

Table 2. *SUVmax of GEP-NET subjects stratified by PFS.*

SUV	PFS length (<18 m, ≥18 m)	N	Mean	Standard deviation	P value
Total SUVmax	Short	11	50.13	27.20	0.112
	Long	14	69.51	30.47	
Primary tumor SUVmax	Short	10	11.89	11.10	0.092
	Long	9	23.74	17.44	
Liver SUVmax	Short	11	14.69	9.17	**0.004***
	Long	13	34.15	17.89	
Mean SUVmax of all lesions	Short	11	15.26	4.84	**0.001***
	Long	14	33.05	14.32	

**P<0.05, GEP-NET, gastroenteropancreatic neuroendocrine tumor; PFS, progression free survival; SUVmax, maximum Standardized Uptake Value*

Table 3. *Characterization of SUVmax in stable/regressive and progressive patients*

PET accumulation	Treatment Outcome	N	SUVmax/Standard Deviation	P value
Total Body SUVmax	Stable/Regression Progression	20 5	57.72±31.78 74.02±19.61	0.289
Mean SUVmax	Stable/Regression Progression	20 5	27.31±15.14 16.85±3.79	**0.011***
Primary tumorSUVmax	Stable/Regression Progression	15 4	17.11±17.03 19.00±6.71	0.833
Liver SUVmax	Stable/Regression Progression	19 5	26.57±19.13 20.12±6.76	0.472

**p<0.05;SUVmax, maximum standardized uptake value*

Table 4. *SUV values of subgroups.*

Parameter	n	SUVmax/Standard deviation	P value
Pancreas Non-pancreas	11 14	24.97±12.68 25.42±15.79	0.939
Gr I Gr II	12 13	26.37±14.76 24.16±14.21	0.707
Ki 67 <3 Ki 67 ≥3	10 15	26.43±14.94 24.42±14.18	0.707
Ki 67 <5 Ki67 ≥5	12 13	24.79±14.17 25.62±14.82	0.887

SUVmax, maximum standardized uptake volume; Gr, grade

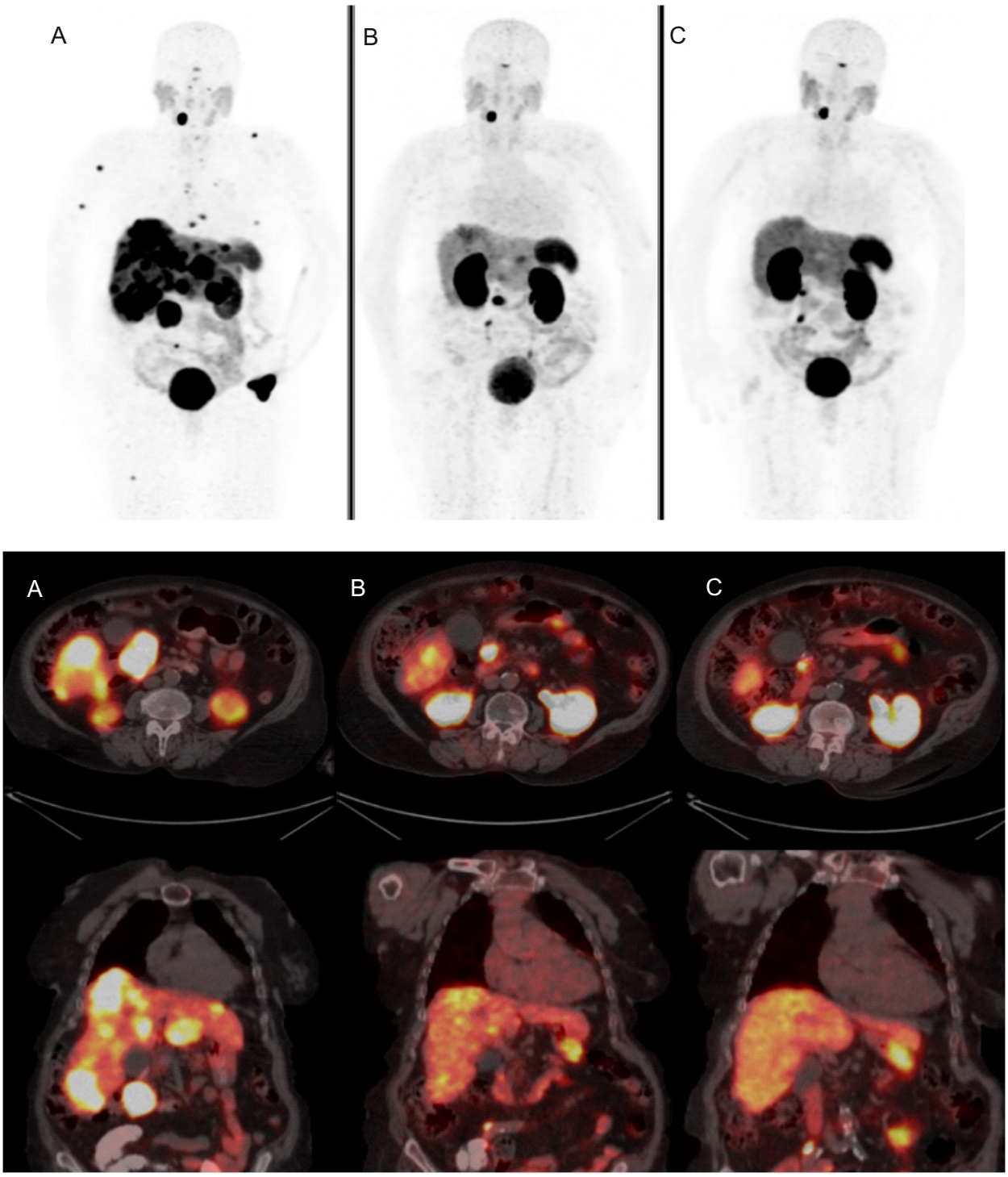

Figure 1. Treatment response of a 77-year-old female patient with GEP-NET. (A) Primary lesion (Arrow), and multiple liver, bone, lymph node metastases were reported in the ^{68}Ga-DOTATATE PET/CT scan of the patient before the treatment. (B) Prominent regression was seen both in quantities and SUVmax, after the first cycle of treatment which consisted of 4 doses. (C) The significant decrease was continued both in dimensions and SUVmax of the primary lesion after the second cycle of the treatment. Total and near-total regression were noted in bone and liver metastases, respectively at the end of the second cycle of the treatment.

Table 5. *PRRT-induced toxicities according to CTCAE v.4.*

Toxicity	N	%
Leukopenia	6	24
Grade 1	1	4
Grade 2	2	8
Grade 3	2	8
Grade 4	1	4
Thrombocytopenia	6	24
Grade 1	2	8
Grade 2	1	4
Grade 3	2	8
Grade 4	1	4
Anemia	5	20
Grade 1	2	8
Grade 2	2	8
Grade 3	1	4
Grade 4	0	0
Nephrotoxicity	2	8
Grade 1	2	8
Grade 2	0	0
Grade 3	0	0

PRRT, peptide receptor radionuclide therapy

was also aimed to examine the sensitivity of molecular ^{68}Ga-DOTATATE PET imaging to predict response.

According to the study protocol, SUV was calculated for the same lesion in each patient. Analyses were based on total and mean SUVmax scores and the scores of the primary tumor and liver metastasis. A significant difference was determined in SUVmax of lesions between patients categorized as longer PFS (>18m) and shorter PFS (<18m). Liver SUVmax and mean SUVmax were higher ($P<0.05$) in patients with longer PFS than in those with shorter PFS. The results of this study indicated that a higher SUVmax was related to a superior result, specifically regarding liver metastases. The mean liver SUVmax and mean SUVmax of all lesions were 34.2 and 33.1, respectively, in patients who showed a good response. These results are consistent with those cited in the literature.Kratochwilet al. (2015) [17] found significantly higher SUVmax in responding metastatic liver lesions (RL) than in those non-responding (NLR) to PRRT (mean liver SUVmax of RL: 33.5, NLR:18.0). It was observed in the current study that the mean SUVmax was significantly higher in patients with stable/regressive disease than in those with progressive disease ($P=0.011$). Gabriel et al. (2009) [28] reported similar results in patients treated with PRRT, although in that study, responder was only accepted as complete, partial or minor response (tumor shrinkage <30%) after the completion of therapy. A significant difference was determined in SUV between responder and stable, and between responder and stable/progressive disease.

However, SUV did not significantly correlate with ORR according to progression. In contrast, Haug et al. (2010) identified SUVmax, ΔSUVmax and ΔSUV T/S (tumor/spleen) as a predictive factor for time to progression in univariate analysis after the end of three months of PRRT [29]. There are a few possible explanations for the variation in quantitative

information, one of which addresses the biological tumor heterogeneity and variable responsiveness of the tumor. Variations in the period between therapy and imaging may be another explanation for SUV instability. Furthermore, genetic variability between cells may affect SSTR expression, and intratumoral or intralesional heterogeneity is an unfavorable condition in terms of PRRT treatment response. Recent studies have shown the crucial role of somatostatin receptor heterogeneity in response to PRRT [30]. However, the focus of the current research was not on heterogeneity, which would have required detailed measurements and calculations.

Two patients in the current study showed tumor growth in the early CT and ^{68}Ga-DOTATATE PET evaluations, but treatment was continued because this finding was not clinically compatible. Finally, both patients responded to treatment. This transient growth was considered a secondary growth due to irritation because of edema in metastasis rather than actual tumor progression. This radiogenic edema was previously described by Brabander et al. (2017) [31] and was called pseudo-progression.This condition is very well defined in immunotherapy response, and it has been stated that the enlargement in tumor size is caused by T cell expansion and extravasation of tumor-infiltrating lymphocytes into the microenvironment [32]. Therefore, the use of irRECIST criteria is recommended in cases with atypical immunotherapy response [33], which may be useful for NET. The critical issue here is that clinicians ought to know and consider in clinical NET management that growth in tumor size does not always imply a real progression.

In our center, we mainly administer four cycles as a standard treatment, and thereafter these patients are followed up every 3-6 months until progression. In this manner, based on the tumor burden and the patient's performance status, the number of cycles can be augmented from three to six. In the current study cohort, seven patients received up to eight repeated cycles. The most prominent rationale was the higher tumor burden in the liver and the persisting symptoms. Yordanova et al. (2017) [34] showed tolerability to repeated doses of ^{177}Lu-DOTATATE with an overall survival benefit. However, no significant relationship between the number of PRRT cycles and PFS was determined in the current study. A recent meta-analysis has shown that salvage PPRT is effective with low toxicity [35]. Nevertheless, the conventional maintenance treatment applied to the current study patients can be considered to have added to the survival of the patients with higher tumor load because most of those patients remained stable on support without progression, indicating a tumor-static impact. Patients receiving a repeated dose of ^{177}Lu-DOTATATE tend to have a better Karnofsky performance score. The prognostic significance of performance status has been previously demonstrated [36]. It seems likely that patient selection could cause such a difference. To better evaluate the survival advantage of prolonged PRRT, a placebo-controlled randomized prospective study is needed.

This study had certain strengths. The population was homogenous, and the patients were scanned before and after therapy with the same tracer using a uniform treatment procedure. However, the study also had a few limitations. The retrospective study design hindered response and prognostic evaluation. Estimations were made based on somatostatin expression without considering intratumoral heterogeneity. Furthermore, it was not possible to calculate overall survival since the follow-up period was relatively short for this slow-growing tumor.

There has been some advancement in treatment approaches over the years. New data will undoubtedly emerge regarding the increase in radiosensitivity with multimodal treatments. Towards the end of the study period, it was considered that other treatment techniques (such as chemotherapy) in combination with PRRT may be better to manage patients with rapid deterioration high tumor burden in prior lines. Therefore, we plan to design a prospective study in NET patients with unfavorable prognosis.

The results of this study showed that the pretreatment SUVmax value could be the most reliable prognostic marker for GEP-NET, and high SUVmax values are associated with better prognosis. Therefore, theranostic approaches and personalizing therapies with widespread dosimetric measurements according to glomerular filtration will help effectivity and prevent toxicity.

The other critical question is the determination of treatment response estimation using pre-treatment imaging. However, it was observed in this study that some patients respond completely to lutetium treatment and had high SUVmax values in metastatic lesions. Thus, SUVmax may not be always correlated with somatostatin receptor expression and response. There may be two possible explanations for this. The first is that the slow course of the disease may cause differentiation in tumor biology, such as in breast and lung cancer. Repeat biopsy or liquid biopsy of new metastases may give more information for a better treatment strategy particularly in late recurrences. For example, when a breast cancer relapses during follow up, receptor status (ER, PR, CerbB2) of the metastasis may be different than that of the original tumor, particularly in late recurrences. After taking a re-biopsy and detecting the difference in receptor status, the application of alternative treatments (Anti hormonal and anti HER-2 therapies) can increase the chances of treatment success [37]. Another example is that in lung cancer patients with epidermal growth factor receptor (EGFR) exon 19 and exon 21 mutations, the EGFR tyrosine kinase inhibitors (TKI) improve response rate and survival. Unfortunately, patients develop disease progression after a while. If repeat biopsy or liquid biopsy is performed, in nearly 50% patients an acquired EGFR T790m mutation is determined and this treatment resistance can be overcome with the new generation TKI [38, 39].The second explanation is that since neuroendocrine tumors are heterogeneous, such as the malignancies described above, somatostatin receptor distribution of metastases may differ. For example, previous treatments before enrollment in the study could have influenced the SSTR status and changed the responsiveness of tumor tissue to radiation therapy. In addition, the different time intervals between last treatment and imaging might be another reason for SUV fluctuation (28). Investigating the common characteristics of the patients who have completely responded to PRRT may pro-

vide new information.

Currently, identification of treatment strategy is based only on SSR expression. Further improvements or combinations of imaging methods may be warranted to address this issue. The liver is both the most common metastasis site in GEP-NET and the most appropriate site worth researching. Further planned investigations should be conducted with larger sample sizes for further clarification.

In conclusion, due to the failure of immunotherapy, PRRT with ^{177}Lu-DOTATATE will continue to be highly recommended as a promising treatment for GEP-NET. In addition, new radioactive agents will be put into practice in the diagnosis and treatment of neuroendocrine tumors. Peptide receptor radionuclide therapy is also expected to be used increasingly in other cancers. Despite the initial high levels of SUV in baseline PET/CT, complete response was still achieved in some of these patients in this study. However, post-treatment follow-up analysis showed early progression particularly in these patients with extensive metastases. Nevertheless, the response was more likely to be longer in patients with higher SUV and with limited metastases regardless of the depth of treatment response. It was hypothesized that the radiation dose per lesion causes the therapeutic index to decrease by reducing whole-body retention with the excretory effect of the kidneys in patients with more extensive disease. The findings of this study suggest that from the population enrolled, it was estimated that ^{177}Lu-DOTATATE could be used more safely in patients with high liver and average SUVmax values. Molecular improvements will more clearly define the relationship between SUVmax and treatment response in the future.

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Ethical Approval

Approval for the study was obtained from the Institutional Review Board of the local Ethics Committee of Gaziantep University. Written informed consent was provided by all the patients for the inclusion of their medical and treatment history within this work.

The authors have no conflict of interests to declare.

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