^{68}Ga-DOTATATE PET/CT for the Early Prediction of Response to Somatostatin Receptor–Mediated Radionuclide Therapy in Patients with Well-Differentiated Neuroendocrine Tumors

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We aimed to evaluate ^{68}Ga-DOTATATE PET/CT for the early prediction of time to progression and clinical outcome after a first cycle of peptide receptor radionuclide treatment (PRRT) in a cohort of patients with well-differentiated neuroendocrine tumors. **Methods:** Thirty-three consecutive patients (22 men and 11 women; mean age ± SD, 57.8 ± 12.1 y) were investigated at baseline and again 3 mo after initiation of the first cycle of PRRT. ^{68}Ga-DOTATATE receptor expression was assessed using 2 measures of standardized uptake value (SUV): maximum SUV (SUV_{max}) and tumor-to-spleen SUV ratio ($SUV_{T/S}$). Percentage change in SUV scores after PRRT relative to baseline (ΔSUV) was calculated. After completing 1–3 cycles of PRRT, patients entered the follow-up study, for estimation of time to progression. According to the Response Evaluation Criteria in Solid Tumors, progression was defined on the basis of contrast-enhanced CT. Clinical symptoms, as well as the tumor markers chromogranin A and neuron-specific enolase, were also recorded during regular follow-up visits. **Results:** The 23 of 31 patients with decreased $SUV_{T/S}$ after the first PRRT cycle had longer progression-free survival than did the 8 of 31 patients with stable or increased scores (median survival not reached vs. 6 mo, $P = 0.002$). For the 18 of 33 patients showing a reduction in SUV_{max}, there was no significant difference in progression-free survival (median survival not reached vs. 14 mo, $P = 0.22$). Multivariate regression analysis identified $SUV_{T/S}$ as the only independent predictor for tumor progression during follow-up. In the 17 of 33 patients with clinical symptoms before PRRT, $\Delta SUV_{T/S}$ correlated with clinical improvement ($r = 0.52$, $P < 0.05$), whereas ΔSUV_{max} did not ($r = 0.42$, $P = 0.10$). Changes in the tumor markers (chromogranin A and neuron-specific enolase) did not predict ΔSUV scores, clinical improvement, or time to progression. **Conclusion:** Decreased ^{68}Ga-DOTATATE uptake in tumors after the first cycle of PRRT predicted time to progression and correlated with an improvement in clinical symptoms among patients with well-differentiated neuroendocrine tumors; $\Delta SUV_{T/S}$ was superior to ΔSUV_{max} for prediction of outcome.

Key Words: neuroendocrine tumors; PET; PET/CT; radionuclide therapy; therapy response; SUV; ^{68}Ga; ^{68}Ga-DOTATATE

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In general, the medical treatment options for well-differentiated neuroendocrine tumors (NETs) are limited. Encouraging results have been reported for peptide receptor radionuclide treatment (PRRT) with somatostatin analogs targeting the somatostatin receptors, which are highly expressed in some NET lines (*1–4*). However, a study considering morphologic criteria for the identification of tumor response reported similar survival rates between NET patients with stable disease or minimal treatment response to PRRT and NET patients exhibiting a partial response (*3*). Other studies showed that despite a clear improvement in symptoms for most patients treated with PRRT, only a small percentage showed a significant decline in tumor size as measured by CT (*1,5*). Furthermore, improved quality of life after PRRT was not clearly associated with a discernible morphologic response to therapy (*4*). These mostly negative findings highlight the need for imaging methods of superior sensitivity for monitoring the response to treatment among NET patients.

PET with ^{18}F-FDG has become established as an indispensable tool for diagnostics and as a surrogate marker in therapy-monitoring studies of various tumor types, such as malignant lymphoma (*6*) and diverse solid tumors (*7–12*).

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In such studies, ^{18}F-FDG PET surpassed CT for assessing the response of gastrointestinal stromal tumors to treatment with tyrosine kinase inhibitors (*13,14*). In the course of such treatment, the ^{18}F-FDG uptake decreased in these tumors, even though the tumor size remained constant for an extended period (*15*). However, the treatment response of NET is notoriously difficult to assess by imaging; these tumors are characterized mostly by a low metabolic activity, preventing their detection with ^{18}F-FDG PET (*16*). However, the characteristically high levels of somatostatin receptor expression present an alternate approach for molecular imaging of NETs. A recent PET study has indicated sensitive detection of NETs with somatostatin analogs such as ^{68}Ga-DOTATATE (*17*). These radiolabeled somatostatin analogs have shown a high uptake in NETs and organs such as the spleen (*18*).

Detection of NET therapy response is likewise difficult; the monitoring of functional parameters may be more reliable than morphologic measurements for assessing therapy response of NETs, as is the case for gastrointestinal stromal tumors. Indeed, Gopinath et al. showed that SPECT with the somatostatin analog ^{111}In-pentetreotide was superior to CT for predicting the clinical outcome of patients with NETs (*19*). However, there have been no studies assessing the value of PET with ^{68}Ga-DOTATATE for predicting therapy response of NETs. Therefore, we aimed in the present study to determine the capabilities of PET with ^{68}Ga-DOTATATE for early prediction of clinical outcome and progression-free survival after the first cycle of PRRT in NET patients. To this end, we evaluated 2 measures of standardized uptake value (SUV)—maximum SUV (SUV_{max}) and tumor-to-spleen SUV ratio ($SUV_{T/S}$)—as quantitative values for predicting time to progression (TTP) and clinical improvement in a series of 33 patients undergoing PRRT. We also compared the SUVs to the blood assays of the NET markers chromogranin A and neuron-specific enolase (NSE).

MATERIALS AND METHODS

Study Population

Thirty-three consecutive patients (22 men, 11 women; mean age ± SD, 57.8 ± 12.1 y; range, 20–72 y) with histologically proven, well-differentiated metastatic NET were included. The patients were treated with 1, 2, or 3 cycles of PRRT: either 3,700 MBq of ^{90}Y-DOTATATE (n = 24), 7,400 MBq of ^{177}Lu-DOTATATE (n = 7), or both (n = 2). Patients not eligible for PRRT were excluded. Patients' clinical data are presented in Table 1. All patients underwent ^{68}Ga-DOTATATE PET/CT before the radiotherapy and again at 3 mo after the first cycle of therapy. The median interval between pretherapeutic PET/CT and therapy was 7 ± 3.5 wk, and the median interval between the first cycle of therapy and posttherapeutic PET/CT was 13 ± 2.3 wk. Eight of 33 patients were pharmaceutically treated with long-acting somatostatin analogs during both the pre- and the posttherapeutic ^{68}Ga-DOTATATE PET/CT (Table 2). Written informed consent was obtained from all patients before the PET examinations. Routine hematologic, liver, and kidney function tests were performed before each therapy, as well as during follow-up visits.

PET Scans

^{68}Ga-DOTATATE was prepared as described previously (*20*). Whole-body PET scans were acquired in 3-dimensional mode (3 min per bed position) using a Gemini PET/CT scanner (Philips) or a Biograph 64 TruePoint PET/CT scanner (Siemens Medical Solutions). In all patients the pre- and posttherapeutic PET scans were performed with the same PET scanner. To validate the comparison between the SUVs obtained with the 2 different scanners, we performed multiple phantom measurements and defined a suit-

TABLE 1. Patient Characteristics

Characteristic	All	Responders	Nonresponders	*P*
Age (y)	57.8 ± 12.1	59.0 ± 10.7	54.9 ± 17.1	0.64
Sex				0.28
Male	20	14	6	
Female	11	9	1	
Previous therapies (e.g., surgery, chemotherapy)	1.8	1.4 ± 1.2	2.6 ± 2.0	0.15
Pretherapeutic SUV_{max}	28.5 ± 15.5	33.0 ± 16.1	19.1 ± 7.1	0.01
TTP (mo)	Not reached	Not reached	6	<0.001
Clinical symptoms	16	10	6	0.2
Chromogranin A				
Elevated	21	15	6	0.28
Pretherapeutic value	5,306	7,420 ± 25,206	2,189 ± 4,178	0.73
NSE				
Elevated	19	13	6	0.95
Pretherapeutic value	39.7	23.9 ± 15.2	24.0 ± 11.3	0.97
Time (wk) between PRRT and...				
Pretherapeutic PET	7.1 ± 3.5	7.0 ± 3.5	7.1 ± 4.1	0.77
Posttherapeutic PET	13.2 ± 2.3	13.4 ± 2.3	13.1 ± 2.5	0.44
Octreotide treatment	5	3	2	0.78

Two of the 33 patients had history of splenectomy. Data are n or mean ± SD. Mann–Whitney U test was used for statistical analyses between responders (decline of $\Delta SUV_{T/S}$) and nonresponders (increase of $\Delta SUV_{T/S}$).

TABLE 2. Clinical Data and SUVs of Study Population

Patient no.	Sex	Age (y)	Primary tumor	Previous therapies	Clinical symptoms		SSA	SUV_{max}	Σ SUV_{max}		ΔSUV_{max}	Σ $SUV_{T/S}$		$\Delta SUV_{T/S}$	TTP
					Baseline	FU			Baseline	FU		Baseline	FU		
1	M	44	Lung	Surgery	Yes	Imp.	Yes	19.4	54.9	62.4	13.7	2.83	2.81	−0.7	NR
2	F	61	Paraganglioma	Surgery, radiation	Yes	NC	Yes	22.4	75.5	71.0	−6.0	3.37	3.43	1.8	NR
3	M	52	CUP	None	Yes	NC	Yes	23.8	77.1	81.4	5.6	3.72	3.63	−2.4	NR
4	M	62	Pancreas	Surgery	Yes	Imp.	Yes	38.4	127.4	102.2	−19.8	6.28	5.03	−19.8	12
5	M	72	Pancreas	None	No	No	No	26.0	32.1	26.0	−19.0	1.55	1.02	−34.5	NR
6	F	49	Retroperitoneal	Surgery, SSA	Yes	Imp.	Yes	42.6	136.8	58.3	−57.4	6.84	2.60	−61.9	NR
7	M	44	Paranasal sinus	Surgery, radiation, chemotherapy	Yes	NC	Yes	18.1	51.7	70.0	35.4	1.48	2.27	53.9	3
8	F	62	Stomach	Surgery	Yes	Imp.	Yes	56.8	138.0	96.4	−30.1	7.50	4.42	−41.0	NR
9	F	57	CUP	None	No	No	No	35.7	163.2	114.9	−29.6	6.61	4.58	−30.7	NR
10	M	68	Ileum	Surgery	Yes	NC	Yes	30.2	88.5	117.1	32.3	3.88	4.01	3.3	8
11	M	68	Pancreas	Surgery, RFA	Yes	Imp.	Yes	46.7	127.9	40.8	−68.1	6.30	1.15	−81.8	NR
12	F	72	Rectum	Surgery, PRRT	No	No	No	6.7	22.9	25.9	13.1	1.21	1.07	−10.8	NR
13	M	70	Lung	Surgery, chemotherapy, SSA, radiation, RFA, TACE	No	No	No	14.3	41.1	45.8	11.4	5.71	6.27	9.9	3
14	M	70	Ileum	Chemotherapy	Yes	Imp.	Yes	25.5	69.6	63.1	−9.3	3.89	4.54	16.8	NR
15	M	60	Lung	Surgery	No	No	No	82.7	314.9	138.9	−55.9	11.13	9.71	−12.7	NR
16	M	63	Pancreas	None	No	No	No	48.5	108.2	73.9	−31.7	11.51	3.55	−69.1	NR
17	M	62	Lung	Surgery	No	No	No	33.6	154.1	44.2	−71.3	12.33	3.09	−74.9	11
18	M	57	Pancreas	None	Yes	NC	Yes	21.1	81.8	115.6	41.3	6.82	9.03	32.5	10
19	M	51	Rectum	Surgery, chemotherapy, TACE, SSA	No	No	No	34.1	79.7	36.4	−54.3	2.68	2.51	−6.5	16
20	M	63	Ileum	RFA	Yes	NC	Yes	17.0	79.9	92.2	15.4	7.83	6.45	−17.7	NR
21	F	250	Ileum	Surgery	No	No	No	16.0	36.7	30.1	−18.0	2.03	1.51	−25.8	12
22	F	42	Ileum	Surgery, TACE, SSA	No	No	No	36.5	163.3	79.8	−51.1	12.19	6.65	−45.4	14
23	M	20	Pancreas	Surgery, chemotherapy, MIBG therapy, SSA	No	No	No	9.4	23.7	53.9	127.4	4.74	7.49	57.9	3
24	M	49	Ileum	Surgery, SIRT, SSA, chemotherapy	Yes	NC	Yes	11.6	58.5	85.9	46.8	9.00	10.48	16.4	6
25	M	53	Rectum	Surgery, PRRT, SSA, radiation	No	No	No	15.4	37.5	65.8	75.5	2.91	2.40	−17.4	14
26	F	66	Ileum	Surgery	No	No	No	38.2	47.0	38.5	−18.1	2.23	1.24	−44.4	NR
27	M	72	Jejunum	Surgery, SSA, INF	No	No	No	36.7	132.2	147.9	11.9	6.09	5.85	−4.0	NR
28	F	67	Pancreas	Surgery	No	No	No	28.1	120.5	41.3	−65.7	18.54	4.44	−76.0	13
29	F	33	Pancreas	Surgery	Yes	Imp.	Yes	25.3	35.3	31.3	−11.3	3.43	2.22	−35.2	NR
30	F	54	Pancreas	Surgery, chemotherapy	No	No	No	9.5	76.6	104.2	36.0			NM	6
31	F	55	Stomach	Surgery, SIRT	Yes	Imp.	Yes	18.8	97.7	126.5	29.5			NM	NR
32	M	66	Ileum	Surgery	Yes	Imp.	Yes	27.7	44.8	59.6	33.0	3.90	2.42	−37.8	NR
33	M	72	Ileum	Surgery, SIRT	Yes	NC	Yes	24.2	116.4	114.0	−2.1	4.87	3.84	−21.2	6

SSA = somatostatin analogues; Σ = sum; FU = follow-up; Imp. = improvement; NR =TTP not reached; NC = no change; CUP = carcinoma of unknown primary; RFA = radiofrequency ablation; TACE = transarterial chemoembolization; MIBG = metaiodobenzylguanidine; SIRT = selective internal radiation therapy; INF = interferon alpha; NM = not measurable.

able correction factor for objects of different sizes on both scanners. The emission sequence was initiated at 60 min after intravenous injection of 200 MBq of ^{68}Ga-DOTATATE, similar to the protocol in other studies using ^{68}Ga-labeled somatostatin analogs (*17,21,22*). Emission data were reconstructed with attenuation correction based on low-dose CT (20 mA, 140 kV, 512 × 512 matrix). All scans were performed in combination with a diagnostic CT scan (100–190 mAs, depending on the region of the scanned organ; 120 kV; 2 × 5 mm collimation; pitch of 1.5) of the head, thorax, abdomen, and pelvis after a 2.5 mL/s intravenous injection of 120 mL of iodine-containing contrast agent (iopromide [Ultravist 300; Schering]). Initiation of this scan was delayed by 50 s in order to depict the venous contrast-medium phase.

Image Evaluation

Two nuclear medicine specialists working side by side in consensus evaluated the PET images using a dedicated software package (Hybrid Viewer; Hermes Medical Solutions). CT data were used for allocation of regions with increased uptake of the radiopharmaceutical to specific morphologic structures. Neither reader was aware of patients' clinical or follow-up data. The peak SUV (SUV_{max}) corrected for body weight was calculated by automatically drawing—around tumors seen on the coregistered axial CT images—a region of interest having a threshold of 50% of the SUV_{max}. We also calculated the SUV of the tumors relative to the maximal splenic uptake by dividing the SUV_{max} of the tumors by the SUV_{max} of the spleen ($SUV_{T/S}$) (Fig. 1). The SUV_{max} of the spleen was likewise calculated by drawing a splenic volume of interest having a threshold of 50% of the respective SUV_{max}. To evaluate the response to therapy, we calculated the percentage changes in ΔSUV_{max} and $\Delta SUV_{T/S}$ relative to the corresponding baseline measurements of up to 3 tumors in 4 organs (liver, lung, lymph nodes, and bone), as well as the primary tumor. Any decrease in SUV_{max} and $SUV_{T/S}$ after the first cycle of therapy was considered a positive response to therapy. Furthermore, we evaluated the SUV_{max} of the most prominent lesion for each patient.

TTP and Clinical Response Evaluation

Patients entered follow-up after completion of the PRRT (1, 2, or 3 cycles). For assessment of TTP, PET/CT follow-up examinations were performed at 3-mo intervals after therapy. A radiologist with 5 y of experience, who had not seen the PET scans or the patients' clinical history, reviewed the contrast-enhanced CT images. For CT evaluation, the unidimensional measurement of the longest axis (or, in lymph nodes, the shortest diameter) was noted in order to assess progression of the primary tumor or the metastases. Every new metastasis noted, and any increase in tumor size of more than 20%, was considered progression, according to the Response Evaluation Criteria in Solid Tumors (*23,24*). Cystic liver metastases were excluded, according to the recommendations of the International Cancer Imaging Society (*25*).

For clinical outcome analysis, patients were asked to report tumor-related symptoms experienced during their inpatient stay immediately before PRRT and at 3 mo after completing PRRT. Any quantitative or qualitative improvement of these symptoms in the course of therapy was noted. We considered only those symptoms clearly related to hormone-secreting NETs, such as flush or diarrhea.

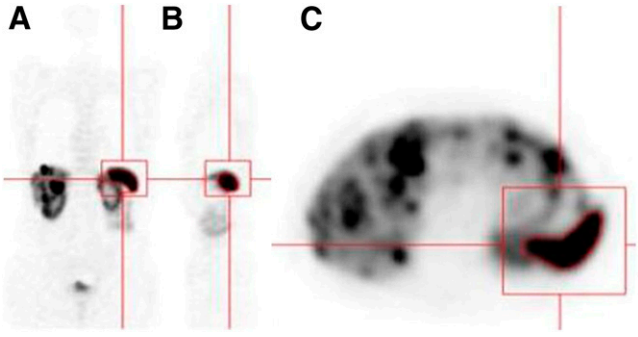

FIGURE 1. Coronal (A), sagittal (B), and axial (C) ^{68}Ga-DOTATATE PET slices showing measurement of splenic SUV_{max} by drawing volume of interest with fixed 50% threshold of SUV_{max}. Inspection of coregistered CT images allows one to exclude the possibility that nonsplenic tissue has intruded into volume of interest.

Tumor Marker

Venous blood samples were drawn within 3 d of the PET/CT study and were stored for subsequent analysis to measure plasma levels of the tumor markers chromogranin A and NSE. Chromogranin A was measured with a solid-phase 2-site immunoradiometric assay purchased from CISbio, and NSE was measured with an electrochemiluminescence immunoassay (Elecsys; Roche). The normal physiologic ranges are less than 98 ng/mL for chromogranin A and less than 16.3 ng/mL for NSE. Of 33 patients, 23 exhibited elevated chromogranin A values and 24 exhibited elevated NSE values. For these patients, the percentage change after therapy was calculated. A decrease of more than 50% or within the reference range was considered a therapy response.

Statistical Analysis

Statistical analyses were performed using the SPSS software package (version 15.0). The Kolmogorov–Smirnov test was performed to prove a gaussian distribution of the values. Pearson correlation coefficients were calculated for the correlations between the different SUV scores. The Kendall τ-test was used to measure the correlation between changes in these scores and clinical improvement. An uncorrected P value of less than 0.05 was assumed to be statistically significant. The t test was used to compare differences in SUV scores of the spleen and to compare the SUV scores of clinical responders. In addition, a receiver-operating-characteristic analysis was used to define a threshold of SUV changes predicting clinical outcome. The TTP of the different groups was compared by Kaplan–Meier analysis with log-rank test. The uni- and multivariate Cox proportional hazards model was used to estimate hazard ratios and 95% confidence intervals for number of PRRT cycles, SUV_{max}, ΔSUV_{max}, and $\Delta SUV_{T/S}$. For $SUV_{T/S}$ evaluation, 2 patients (patients 30 and 31) with a history of splenectomy were excluded. Quantitative data are presented as mean ± SD.

RESULTS

Tumor SUV_{max} ranged from 6.7 to 82.7 (mean, 28.5 ± 15.5) before PRRT and from 7.4 to 43.7 (mean, 22.9 ± 9.4) after PRRT. Summed SUV_{max} ranged from 22.9 to 314.9 (mean, 91.4 ± 58.2) before PRRT and from 25.9 to 147.9 (mean, 74.4 ± 34.5) after PRRT. Summed $SUV_{T/S}$ ranged

from 1.21 to 18.54 (mean, 5.01 ± 3.4) before PRRT and from 1.02 to 10.48 (mean, 4.18 ± 2.5) after PRRT.

Splenic SUV_{max} ranged from 5.0 to 35.5 (mean, 18.4 ± 7.7). Mean splenic SUV_{max} was lower before therapy (range, 5.0–35.0; mean, 17.3 ± 7.4) than after therapy (range, 7.2–35.5; mean, 19.6 ± 8.0) ($P = 0.05$); individual pre- and posttherapeutic SUV_{max} correlated ($r = 0.62$; $P < 0.001$), and SUV_{max} correlated with $SUV_{T/S}$ ($r = 0.64$, $P < 0.001$).

TTP

Median follow-up time was 22.3 ± 5.1 mo (range, 13–34 mo). Fifteen patients showed disease progression, with a median TTP of 10.0 ± 4.4 mo (range, 3–16 mo). There was no significant difference in TTP between patients treated pharmacologically and those without such treatment ($P = 0.70$; log rank test). The 23 patients with decreasing $SUV_{T/S}$ after therapy had significantly longer TTP than did those without an $SUV_{T/S}$ decrease (median TTP not reached vs. 6 mo, $P = 0.002$) (Figs. 2 and 3). Differences in progression-free survival were also significant when the comparison was only between patients with ($P < 0.05$) and without ($P < 0.05$) octreotide treatment. Differences in TTP as predicted by ΔSUV_{max} were not significant (median TTP not reached vs. 14 mo, $P = 0.22$). According to the Cox proportional hazards model, we identified the $\Delta SUV_{T/S}$ as the only predictor of TTP in both univariate ($P = 0.006$) and multivariate analyses ($P = 0.03$; Table 3). Additionally, the SUV_{max} was identified as a predictor of TTP in univariate analysis only ($P = 0.04$).

Clinical Outcome

Seventeen of 33 patients showed clinical symptoms of metastatic NET, notably flush or diarrhea. Among these 17 symptomatic patients, clinical improvement showed a slightly higher correlation with $\Delta SUV_{T/S}$ ($r = 0.52$, $P < 0.05$) than with ΔSUV_{max} ($r = 0.42$, $P = 0.10$). Patients showing clinical improvement exhibited a significant decrease in $SUV_{T/S}$ (33% ± 32%; range, −82% to 17%; $P = 0.02$), with a concomitant significant decrease in SUV_{max} (19% ± 34%; range, −68% to 33%; $P = 0.02$) (Fig. 4). Patients without clinical improvement showed an 8% ± 25% increase (range, −21% to 54%) in $SUV_{T/S}$, whereas SUV_{max} increased by 22% ± 21% (range, −6% to 47%). According to the receiver-operating-characteristic analysis, a ΔSUV_{max} threshold of −4% predicted an improvement in clinical symptoms with 75% sensitivity and 100% specificity, whereas a $\Delta SUV_{T/S}$ threshold of −19% also had 75% sensitivity but only 87.5% specificity.

Tumor Markers

There was no significant correlation between change in chromogranin A and either ΔSUV_{max} ($r = 0.02$, $P = 0.93$) or $\Delta SUV_{T/S}$ ($r = 0.12$, $P = 0.60$), nor did the change in NSE levels significantly correlate ($r = 0.31$, $P = 0.17$, and $r = 0.34$, $P = 0.15$, respectively).

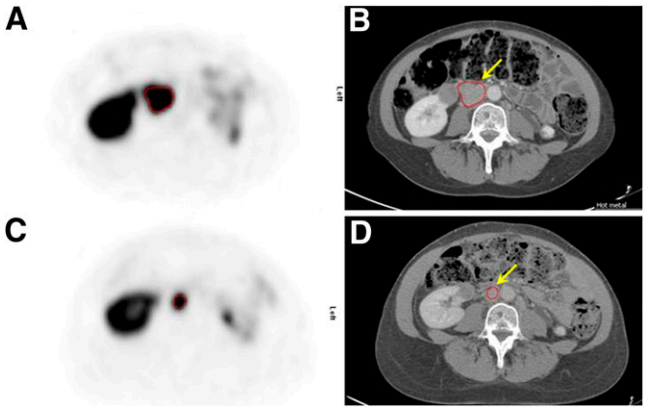

FIGURE 2. Pretherapeutic axial PET (A) and CT (B) slices, compared with posttherapeutic PET (C) and CT (D) slices, showing abdominal lymph node metastasis (arrow) of patient 6. Both SUV_{max} (−55%) and $SUV_{T/S}$ (−60%) decreased markedly after PRRT. This patient has been progression-free for 28 mo.

DISCUSSION

Early prediction of therapy response in tumors is essential to guide therapy and avoid the side effects and costs incurred by ineffective therapies. There is a particular need for a sensitive molecular imaging marker for patients with NET, because CT-based assessment of therapy response does not correlate well with progression-free survival, clinical outcome, or quality of life (*3,4,19*). Although the utility of ^{18}F-FDG PET in assessing therapy response for many other tumors (*6,7,9,10,26,27*) does not generalize to NET, we anticipated that ^{68}Ga-DOTATATE PET would target a specific NET marker, overexpression of somatostatin receptor.

To our knowledge, this was the first study evaluating ^{68}Ga-DOTATATE PET/CT in the prediction of progression-free survival and clinical outcome in patients after PRRT. Patients with a decline in $SUV_{T/S}$ after finishing the first cycle of PRRT had a significant longer TTP than did patients without favorable $SUV_{T/S}$ changes, suggesting that this parameter has a potential role for the early prediction of outcome in patients with well-differentiated NET. Interestingly, ΔSUV_{max} did not emerge as a significant predictor of TTP, either through Kaplan–Meier statistics or the Cox regression hazard model. That finding is in line with recently published results by Gabriel et al. (*28*), who similarly found that the ΔSUV_{max} for ^{68}Ga-DOTATOC PET was not useful for assessing therapy response in a series of 46 NET patients. Their ΔSUV_{max} fluctuated randomly after 2–7 cycles of PRRT. However, there was in our study a (not statistically significant) trend toward a longer TTP with decreasing SUV_{max}. A longer follow-up time might potentially have increased the level of significance also for SUV_{max}. In general, the validity of this method of calculating SUV_{max} is not clearly established for PET studies with

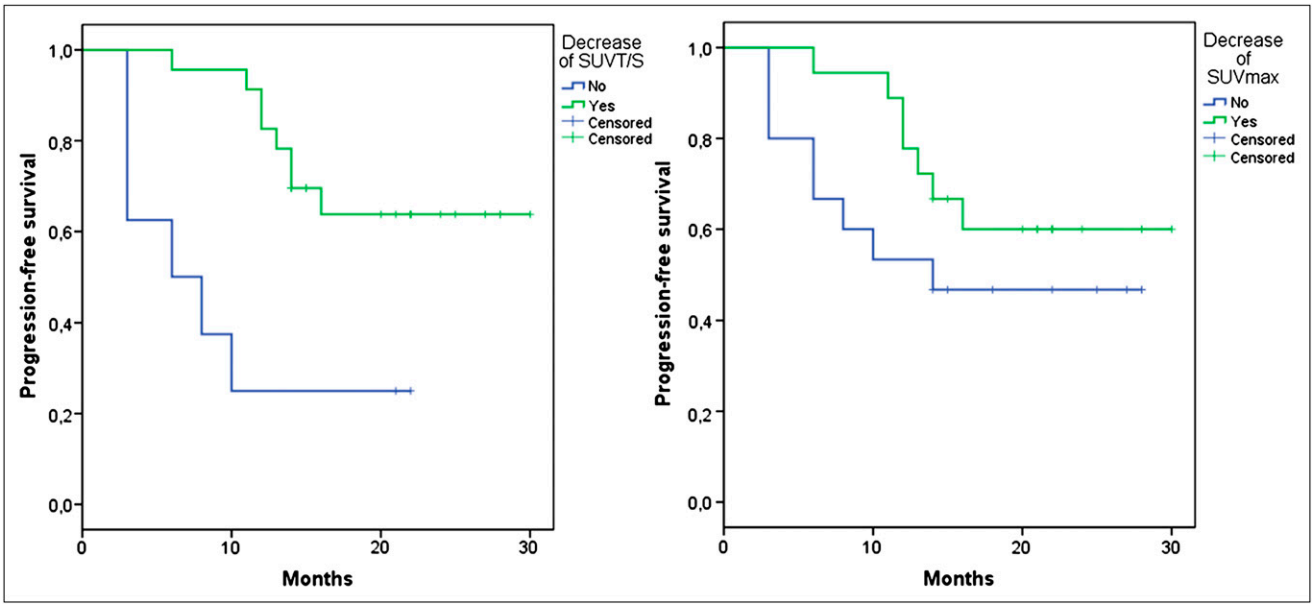

FIGURE 3. Kaplan–Meier progression-free survival curves as functions of $\Delta SUV_{T/S}$ ($P = 0.002$) (left) and ΔSUV_{max} ($P = 0.22$) (right). *P* values were calculated with log-rank test.

^{68}Ga-DOTATATE or other somatostatin receptor ligands. Particularly in the context of PRRT, several cycles of which usually impairs renal function (*29*), SUV_{max} might be spuriously influenced by a therapy-related alteration of plasma tracer clearance, occurring independently of tumor progression. Furthermore, as there is almost no uptake of ^{68}Ga-DOTATATE in the body except in tumors, the spleen, and a few other organs, a large percentage of the injected dose tends to concentrate in these tissues. If the treatment is successful in reducing uptake of tracer specifically in the tumor, more tracer will be available for physiologic uptake in the unaffected spleen and other organs. Under this circumstance, the calculation of SUV normalized to the injected dose and body weight is not exactly equivalent to normalizing to the dose available to any specific tumor or organ. Because of this potential confounding of estimates based on maximal uptake, we additionally defined a tumor-to-spleen ratio ($SUV_{T/S}$), which proved to have only a moderate correlation with individual estimates of SUV_{max}, suggesting a certain pharmacodynamic invariance of our reference tissue index.

Despite the favorable properties of $\Delta SUV_{T/S}$ for the prediction of TTP and clinical outcome, the possibility must be considered that this quantitative parameter was itself influenced by PRRT. Besides potential effects of PRRT on the expression and density of somatostatin receptors on the surface of the NET cells, we noted in the present study that PRRT increased ^{68}Ga-DOTATATE uptake by the spleen. Partly because of this alteration, the number of responders was higher for $\Delta SUV_{T/S}$ than for ΔSUV_{max}. Nonetheless, $\Delta SUV_{T/S}$ proved to be superior to ΔSUV_{max} in predicting TTP and clinical outcome. We speculate that SUV_{max} might be corrected for the effects of PRRT on renal clearance of tracer by normalizing to the SUV_{max} of the spleen, resulting in greater prognostic value. Furthermore, decreased ^{68}Ga-DOTATATE uptake in tumors could theoretically reflect dedifferentiation of NET cells, given that somatostatin receptor expression depends on the grade of differentiation

TABLE 3. Analysis of SUVs as Predictors of TTP

	Univariate analysis		Multivariate analysis		
Variable	Hazard ratio	*P*	Hazard ratio	*P*	Regression coefficient
SUV_{max}	0.95 (0.908–0.996)	0.04	0.96 (0.91–1.01)	NS	−0.04
ΔSUV_{max}	0.54 (0.19–1.49)	NS			
$\Delta SUV_{T/S}$	0.22 (0.07–0.65)	0.006	0.29 (0.10–0.90)	0.03	−1.24
Number of PRRT cycles	0.59 (0.22–1.60)	NS			

NS = not statistically significant.

Data in parentheses are 95% confidence intervals. SUV_{max} is for most prominent tumor before PRRT. ΔSUV_{max} and $\Delta SUV_{T/S}$ are for responder vs. nonresponder.

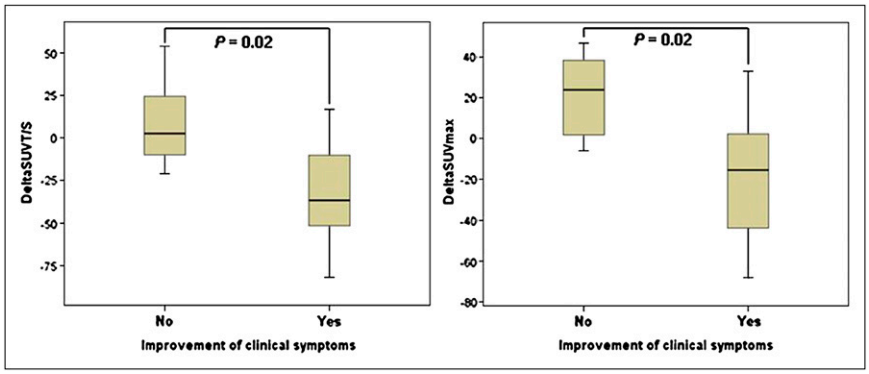

FIGURE 4. Distribution of $\Delta SUV_{T/S}$ (P = 0.02) (A) and ΔSUV_{max} (P = 0.02) (B) of patients with reference to clinical improvement after PRRT. Boxes represent second and third quartiles. Bar within each box refers to mean value, and bars above and below each box indicate range.

of NET (*30*). In this scenario, rapid tumor growth could have led to shortened TTP. For early detection of dedifferentiation, combination PET/CT instead of PET alone is highly recommended.

Interestingly, univariate regression analysis identified pretherapeutic SUV_{max} as an accurate predictor for TTP, perhaps insofar as high receptor density may predispose to an optimal response to PRRT. This finding is in line with a previously published study that reported a higher response rate to PRRT in 310 NET patients exhibiting a high uptake in conventional somatostatin scintigraphy (*2*). This correlation has not been proved for ^{68}Ga-DOTATATE PET.

In addition to the prediction of progression, a second major endpoint of the present study was the improvement of clinical symptoms, which is a major goal of the predominantly palliative therapies in metastatic NET. We found that a decline in $SUV_{T/S}$ correlated significantly (and slightly better than the SUV_{max}) with the improvement of clinical symptoms. The value of ^{68}Ga-DOTATATE PET for prediction of clinical improvement during follow-up is consistent with an earlier report of Gopinath et al., who found a close correlation between the change in functional volume of NET assessed with ^{111}In-pentetreotide SPECT and the improvement of clinical symptoms (*19*). Furthermore, ^{111}In-pentetreotide SPECT proved to be clearly superior to CT in that study. We expect that ^{68}Ga-DOTATATE PET imparts advantages over ^{111}In-pentetreotide SPECT because of the higher affinity of the PET ligand for the constitutively expressed SSRT type 2, and given the superior spatial resolution of PET. Although the 2 ligands have not yet been compared directly, our finding that decreased ^{68}Ga-DOTATATE uptake predicts clinical improvement emphasizes the link between decrease in SUV and improvement in NET symptoms.

In an animal study, chromogranin A secretion correlated strongly with the reduction of tumor volume after PRRT (*31*), but we did not find any relationship between chromogranin A or NSE levels and patient outcome. It might well be that the 3-mo follow-up after PRRT was too brief an interval for detecting true responses by tumor markers, especially given that there may have been a paradoxic elevation (i.e., due to treatment-related secretion) in the early posttreatment reassessment. Basically, the plasma chromogranin A level had low specificity for predicting changes in tumor size among human gastrinoma patients and varied considerably from day to day (*32*). In several previous clinical studies, chromogranin A levels failed to correlate with the NET mass (*33–38*). In fact, chromogranin A levels have been shown to reflect hepatic tumor burden (*39*). Thus, the serum chromogranin A level seems generally unsuited for assessing palliative therapy response in well-differentiated NET.

Regarding study limitations, it might be argued that a single, uniform PRRT protocol should have been assessed. However, the aim of this study was to evaluate the ability of ^{68}Ga-DOTATATE PET to predict progression, not to evaluate the merits of a particular treatment. Despite the different treatment protocols, the TTP found in our study is in line with other studies (*3,40*). Furthermore, we found no significant correlation between the number of PRRT cycles and TTP.

Treatment of part of our patient group with long-acting somatostatin analogs may constitute a limitation of this study, given that this treatment may conceivably influence SUV_{max} both in tumors and in the spleen. However, we are unaware of any formal demonstration of the conjectural effect of somatostatin analogs on the SUV of ^{68}Ga-DOTATATE. In any event, our patients were medicated during both the pre- and the posttherapeutic PET scans. Therefore, assuming that the effects of those somatostatin analogs were uniform over time, scores should have been influenced in the same way, with no bias on $\Delta SUV_{T/S}$ scores.

CONCLUSION

This study suggests that ^{68}Ga-DOTATATE PET/CT may contribute usefully to the early prediction of TTP and to the prediction of treatment outcome in patients with well-differentiated NET undergoing PRRT. $\Delta SUV_{T/S}$ proved superior to baseline SUV_{max} and ΔSUV_{max} for the prediction of treatment outcome.

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