Original article

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The prognostic role of whole-body volumetric ^{68}GA-DOTATATE PET/computed tomography parameters in patients with gastroenteropancreatic neuroendocrine tumor treated with ^{177}LU-DOTATATE

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Objective **The aim of this study is to evaluate the prognostic role of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and quantitative ^{68}Ga-DOTATATE PET/computed tomography parameters such as maximum standardized uptake value (SUVmax), mean SUV (SUVmean), DOTATATE tumor volume (DTV), total lesion DOTATATE (TLD) in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) treated with ^{177}Lu-DOTATATE.**

Material and method **Our retrospective study included 21 patients with GEP-NETs treated with ^{177}Lu-DOTATATE between January 2017 and January 2022. SUVmax, SUVmean, SUVmax/spleenSUVmax (SUVmax/Sx), DTV, TLD, SUVmean/spleenSUVmean (SUVmean/Sm), TLD/Sm values were calculated and recorded for all patients before and after ^{177}Lu-DOTATATE treatment.**

Results **A total of 319 metastases were detected in the patients included in the study, and a total of 68 target lesions were selected. In univariant Cox regression analysis, TLD/Sm percent change (ΔTLD/Sm) was found to be statistically significant on overall survival (OS) ($P = 0.044$). The 3-year survival in nonresponders was 50% ($P = 0.034$) based on ΔSUVmax/Sx values, 50% ($P = 0.002$) based on RECIST values, 50% based on ΔTDTV + new lesion values ($P = 0.033$), and according to ΔTTLD + new lesion values, it was 66% ($P = 0.030$).**

Conclusion **In our study, we showed that SUVmax/Sx, RECIST, ΔTDTV + new lesion, and ΔTTLD + new lesion parameters can predict OS in the evaluation of response to treatment. *Nucl Med Commun* 44: 509–517**

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Keywords: **^{68}Ga-DOTATATE, gastroenteropancreatic neuroendocrine tumors, ^{177}Lu-DOTATATE, PET/computed tomography**

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Introduction

The incidence and prevalence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have increased considerably in recent years [1]. GEP-NETs are a group of neoplasms originating from neuroendocrine cells and ranging from well differentiated neuroendocrine tumors to poorly differentiated aggressive neuroendocrine carcinomas [2]. ^{177}Lu-DOTATATE is a peptide receptor radionuclide therapy (PRRT) agent used in the treatment of somatostatin receptor-positive, unresectable, or metastatic GEP-NETs [3]. ^{177}Lu-DOTATATE is a treatment option with a high response rate and long median progression-free survival (PFS) in the heterogeneous patient population with NET [4]. Although PRRT is effective in most cases, approximately 15–30% of patients develop disease progression during PRRT, and early detection of this condition may allow the patient to benefit from different treatment combinations and alternative treatments [5]. In the treatment of ^{177}Lu-DOTATATE, the requirement to identify patients who will benefit from this treatment is an important unmet need [6]. Recently, biochemical evaluation of tumor markers such as chromogranin A has also been insufficient to predict response to PRRT therapy. Although promising and innovative approaches such as NET TEST have been proposed, they are very costly and not easily available [7,8].

Most NETs overexpress somatostatin receptors (SSTRs) on the cell surface and allow SSTR-based imaging with ^{68}Ga-DOTATATE PET/computed tomography (CT). In recent years, ^{68}Ga-DOTATATE PET/CT has become the preferred imaging modality for diagnosis, staging, and patient selection for ^{177}Lu-DOTATATE treatment in patients with NET [9]. Although the maximum standardized uptake value (SUVmax) determined by ^{68}Ga-DOTATATE-PET/CT was suitable for a rough estimate, it was not considered an ideal predictive parameter because somatostatin receptor heterogeneity in tumors is a problematic factor for the sensitive assessment of treatment response [10]. In a recent study, tumor volume obtained from ^{68}Ga-DOTATATE-PET/CT was

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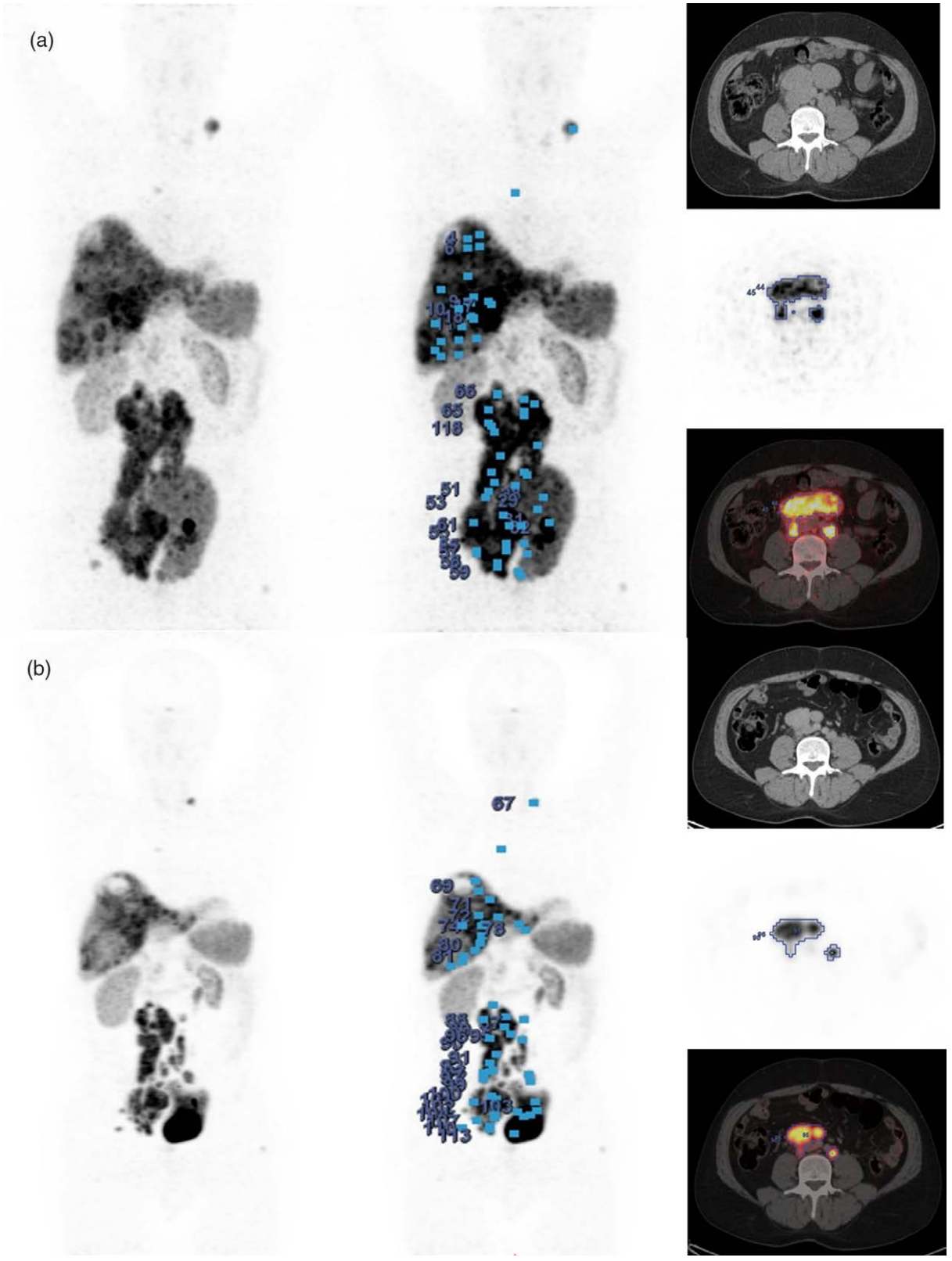
Fig. 1



A 50-year-old male patient with metastatic well differentiated liver NET (G1, Ki 67 8%) who had a partial response to treatment according to RECIST 1.1 after four cycles of ^{177}Lu-DOTATATE therapy. (a) Pretreatment HSUVmax1 : 35.83, TDTV1 : 346.1, TTLD1 : 5882.6 (MIP, PET, and fusion image with and without VOIs). (b) Posttreatment HSUVmax2 : 27.48, TDTV2 : 242.7, TTLD2 : 2877.48 (MIP, PET, and fusion image with and without VOIs). HSUVmax, highest SUVmax; MIP, maximum intensity projection; RECIST, Response Evaluation Criteria in Solid Tumors; SUVmax, maximum standardized uptake value; TDTV, DOTATATE tumor volume; TTLD, total lesion DOTATATE; VOIs, volumes of interest.

Table 1 Comparison of descriptive parameters

	N	Mean ± SD	Median (min–max)
Age	21	60.43 ± 9.75	58 (44–86)
Number of cures	21	4.19 ± 0.60	4 (4–6)
Ki 67	21	11.5 ± 13.84	4.5 (2–45)
HSUVmax1	21	47.43 ± 25.5	44.3 (10.7–121.9)
HSUVMax/Sx1	21	2.04 ± 0.97	1.85 (0.32–4.48)
HSUVmax2	21	38.4 ± 18.59	35.6 (0–77.1)
ΔHSUVmax	21	−88.98 ± 5.92	−90.41 (−100 to 75.01)
ΔHSUVmax/Sx	21	−0.8 ± 53.76	−18.82 (−100 to 122.52)
HSUVMax/Sx2	21	1.94 ± 1.08	1.66 (0–4.34)
HSUVmean1	21	26.01 ± 12.6	24.2 (8.8–56.1)
HSUVmean/Sm1	21	1.61 ± 0.62	1.66 (0.36–2.75)
HSUVmean2	21	20.58 ± 7.72	22.1 (0–33.1)
HSUVmean/Sm2	21	1.45 ± 0.66	1.48 (0–2.95)
ΔSUVmean	21	−10.78 ± 48.22	−10 (−100 to 118.94)
ΔSUVMEN/Sm	21	−6.85 ± 40.83	−10.71 (−100 to 76.73)
TDTV1	21	207.22 ± 307.54	97.46 (1.34–1362.14)
TDTV2	21	185.09 ± 333.11	110.05 (0–1545.17)
TLD1	21	3595.01 ± 4541.73	2183 (11.9–19767.26)
TLD/Sm1	21	263.60 ± 410.23	135.22 (0.49–1847.41)
TLD2	21	3216.66 ± 5931.06	1355.96 (0–27450.92)
TLD/Sm2	21	216.26 ± 380.84	97.59 (0–1771.03)
ΔDTVD	21	−21.45 ± 42.03	−28.27 (−100 to 78.26)
ΔTLD	21	−30.05 ± 42.23	−35.07 (−100 to 48.11)
ΔTLD/Sm	21	−23.89 ± 51.49	−31.01 (−100 to 86.58)
PFS	21	23.11 ± 14.87	17.46 (5.6–61.23)
OS	21	31.46 ± 16.11	27.66 (9.07–69.13)

Δ, percent change; HSUVmax, highest SUVmax; OS, overall survival; PFS, progression-free survival; SUVmax, maximum standardized uptake value; SUVMax/Sx; SUVmax/spleenSUVmax; SUVmean/Sm, SUVmean/spleenSUVmean; TDTV, total DOTATATE tumor volume; TLD, lesion DOTATATE.

reported to be independently associated with PFS and disease-specific mortality in patients with NET. It has been shown that higher tumor volumes are associated with shorter PFS and higher disease-specific mortality [11]. The Response Evaluation Criteria in Solid Tumors (RECIST) criteria do not appear to be the best option for assessing treatment response in NET; however, some guidelines recommend the use of CT and MRI for the initial diagnosis and follow-up of these tumors [12,13].

The aim of this study is to evaluate the prognostic role of RECIST 1.1 and quantitative parameters obtained from ^{68}Ga-DOTATATE PET/CT such as SUVmax, SUVmean, DOTATATE tumor volume (DTV), and total lesion DOTATATE (TLD) in patients with GEP-NET treated with ^{177}Lu-DOTATATE.

Material and method

Patient selection and study design

Our retrospective study included 21 patients with GEP-NET treated with ^{177}Lu-DOTATATE between January 2017 and January 2022. Inclusion criteria: patients with a histopathological diagnosis of Grade I-II-III GEP-NET and showing high SSTR expression in ^{68}Ga-DOTATATE-PET/CT (Krenning scores 3 and 4) [14], Eastern Cooperative Oncology Group performance score of 0–2 and life expectancy of more than 3 months were included. Exclusion criteria: patients whose data could not be reached, who had additional malignancies and heart failure, who refused PRRT treatment, who could not complete PRRT treatment, who were pregnant, or who were still breastfeeding were not included in the study. In addition, patients with creatinine clearance below <40 ml/min, hemoglobin < 8 g/dl, platelets < 75×10^9/l, leukocytes < 2×10^9/l, total bilirubin value more than three times the normal, albumin < 30 g/dl, prothrombin time more than 1.5 times were excluded from the study. The patient's age, clinical stage, tumor grade, and Ki-67 index were recorded. Approval from the local ethics committee was obtained (approval no: 232/2022). All patients or their relatives provided verbal and written informed consent.

Application of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy

All patients were treated with four or six cycles of 7.4 GBq ^{177}Lu-DOTATATE treatment at 8-week intervals; 105 cc of lactated Ringer's solution, 5 cc of magnesium sulfate, and 1 ampoule of metoclopramide were added into 390 ml of nephramine 5% solution and it was given by intravenous infusion for a total of 30 min. ^{177}Lu-DOTATATE was diluted to 100 cc and it was given by intravenous infusion for 30 min. Immediately after, three times of 500 cc solution was prepared and given by intravenous infusion for a total of 3 h. Patients underwent ^{68}Ga-DOTATATE-PET/CT imaging approximately 3 months after the last cycle of ^{177}Lu-DOTATATE therapy.

^{68}Ga-DOTATATE-PET/CT imaging protocol

All images were obtained using Discovery IQ 4 ring 20 cm axial field of view (FOV) PET/CT (GE Healthcare, Milwaukee, Wisconsin, USA). Sixty minutes after 2MBq/kg ^{68}Ga-DOTATATE injection, whole-body images were taken from the vertex to the middle of the thigh at the first hour. After CT images (CT parameters: 120 kV, 80 mAs/slice, 700 mm transaxial FOV, no gap, 64 × 0.625 mm collimation, pitch 1.4, 0.5 s rotation time, 3.3 mm slice thickness, 512 × 512 matrix), PET images (PET parameters: 3D FOV 20 cm, ordered subset expectation maximization algorithm five iterations/12 subsets, full width at half maximum 3 mm) were taken at the bedside at 2.5 min in the same position to include the same regions. All patients without contraindications were given intravenously 1.5 ml/kg non-ionic contrast material before CT imaging. All patients were asked to drink water before PET/CT imaging and urinated immediately before imaging.

Evaluation of images

All ^{68}Ga-DOTATATE PET/CT images were reviewed on Advantage Workstation software version 4.7 (GE Healthcare) by two specialists with at least 10 years of PET/CT experience. After excluding physiological uptake sites and benign lesions, increased uptake of DOTATATE above the background level and considered malignant by both specialists were accepted

Table 2 Evaluation of treatment response criteria

	Frequency	Percent	Valid percent	Cumulative percent
ΔSUVmax				
CR	1	4.8	4.8	4.8
PR	20	95.2	95.2	100.0
Total	21	100.0	100.0	
ΔSUVmax/Sx				
CR	1	4.8	4.8	4.8
PR	4	19.0	19.0	23.8
Stable disease	10	47.6	47.6	71.4
Progressive disease	6	28.6	28.6	100.0
Total	21	100.0	100.0	
ΔSUVmean				
CR	1	4.8	4.8	4.8
PR	5	23.8	23.8	28.6
Stable disease	11	52.4	52.4	81.0
Progressive disease	4	19.0	19.0	100.0
Total	21	100.0	100.0	
ΔSUVmean/Sm				
CR	1	4.8	4.8	4.8
PR	3	14.3	14.3	19.0
Stable disease	13	61.9	61.9	81.0
Progressive disease	4	19.0	19.0	100.0
Total	21	100.0	100.0	
ΔTTLD				
CR	1	4.8	4.8	4.8
PR	10	47.6	47.6	52.4
Stable disease	7	33.3	33.3	85.7
Progressive disease	3	14.3	14.3	100.0
Total	21	100.0	100.0	
ΔTTLD/Sm				
CR	1	4.8	4.8	4.8
PR	10	47.6	47.6	52.4
Stable disease	7	33.3	33.3	85.7
Progressive disease	3	14.3	14.3	100.0
Total	21	100.0	100.0	
RECIST				
CR	1	4.8	4.8	4.8
PR	3	14.3	14.3	19.0
Stable disease	11	52.4	52.4	71.4
Progressive disease	6	28.6	28.6	100.0
Total	21	100.0	100.0	
ΔTDTV + new lesion				
Responder	16	76.2	76.2	76.2
Nonresponder	5	23.8	23.8	100.0
Total	21	100.0	100.0	
ΔSUVmax/Sx				
Responder	15	71.4	71.4	71.4
Nonresponder	6	28.6	28.6	100.0
Total	21	100.0	100.0	
ΔSUVmean				
Responder	15	71.4	71.4	71.4
Nonresponder	6	28.6	28.6	100.0
Total	21	100.0	100.0	
ΔSUVmean/Sm				
Responder	17	81.0	81.0	81.0
Nonresponder	4	19.0	19.0	100.0
Total	21	100.0	100.0	
ΔTTLD				
Responder	18	85.7	85.7	85.7
Nonresponder	3	14.3	14.3	100.0
Total	21	100.0	100.0	
ΔTTLD/Sm				
Responder	18	85.7	85.7	85.7
Nonresponder	3	14.3	14.3	100.0
Total	21	100.0	100.0	
RECIST				
Responder	15	71.4	71.4	71.4
Nonresponder	6	28.6	28.6	100.0
Total	21	100.0	100.0	
ΔTDTV				
Responder	19	90.5	90.5	90.5
Nonresponder	2	9.5	9.5	100.0
Total	21	100.0	100.0	

Δ, percent change; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SUVmax, maximum standardized uptake value; SUVMax/Sx; SUVmax/spleenSUVmax; SUVmean/Sm, SUVmean/spleenSUVmean; TDTV, DOTATATE tumor volume; TTLD, total lesion DOTATATE.

Table 3 Univariate Cox regression analysis for overall survival

				95% CI for odds ratio	
	B (SE)	*P* value	Odds ratio	Lower	Upper
Age	−0.017 (0.072)	0.810	0.983	0.853	1.132
HSUVmax1	−0.045 (0.034)	0.189	0.956	0.894	1.022
HSUVMax/Sx1	−0.638 (0.571)	0.264	0.528	0.172	1.619
HSUVmax2	0.033 (0.031)	0.292	1.033	0.972	1.098
ΔHSUVmax	0.107 (0.102)	0.296	1.113	0.911	1.360
ΔHSUVMAX/Sx	0.009 (0.007)	0.230	1.009	0.994	1.024
HSUVMax/Sx2	0.806 (0.654)	0.217	2.240	0.622	8.065
HSUVmean1	−0.078 (0.067)	0.243	0.925	0.811	1.055
HSUVmean/Sm1	−0.767 (0.787)	0.329	0.464	0.099	2.169
HSUVmean2	0.066 (0.103)	0.525	1.068	0.872	1.308
HSUVmean/Sm2	1.044 (1.022)	0.307	2.840	0.383	21.064
HSUVmean/Sm2	1.044 (1.022)	0.307	2.840	0.383	21.064
ΔSUVmean/Sm	0.015 (0.014)	0.259	1.015	0.989	1.043
TDTV1	0.001 (0.001)	0.474	1.001	0.999	1.002
TDTV2	0.001 (0.001)	0.378	1.001	0.999	1.002
TLD1	0.000 (0.000)	0.601	1.000	1.000	1.000
TLD/Sm1	0.000 (0.001)	0.587	1.000	0.999	1.002
TLD2	0.000 (0.000)	0.401	1.000	1.000	1.000
TLD/Sm2	0.001 (0.001)	0.379	1.001	0.999	1.002
ΔDTVD	0.021 (0.011)	0.067	1.021	0.999	1.044
ΔTLD	0.020 (0.011)	0.075	1.021	0.998	1.044
ΔTLD/Sm	0.023 (0.011)	0.044	1.023	1.001	1.046
ΔSUVmax/Sx	9.651 (91.623)	0.916	15 530.000	0.000	1.510
RECIST	19.196 (151.204)	0.899	217 218.000	0.000	1.100

Cox regression enter method.

Δ, percent change; CI, confidence interval; HSUVmax, highest SUVmax; RECIST, Response Evaluation Criteria in Solid Tumors; SE, standard error; SE, standard error; SUVmax, maximum standardized uptake value; SUVMax/Sx; SUVmax/spleenSUVmax; SUVmean/Sm, SUVmean/spleenSUVmean; TDTV, DOTATATE tumor volume; TLD, lesion DOTATATE.

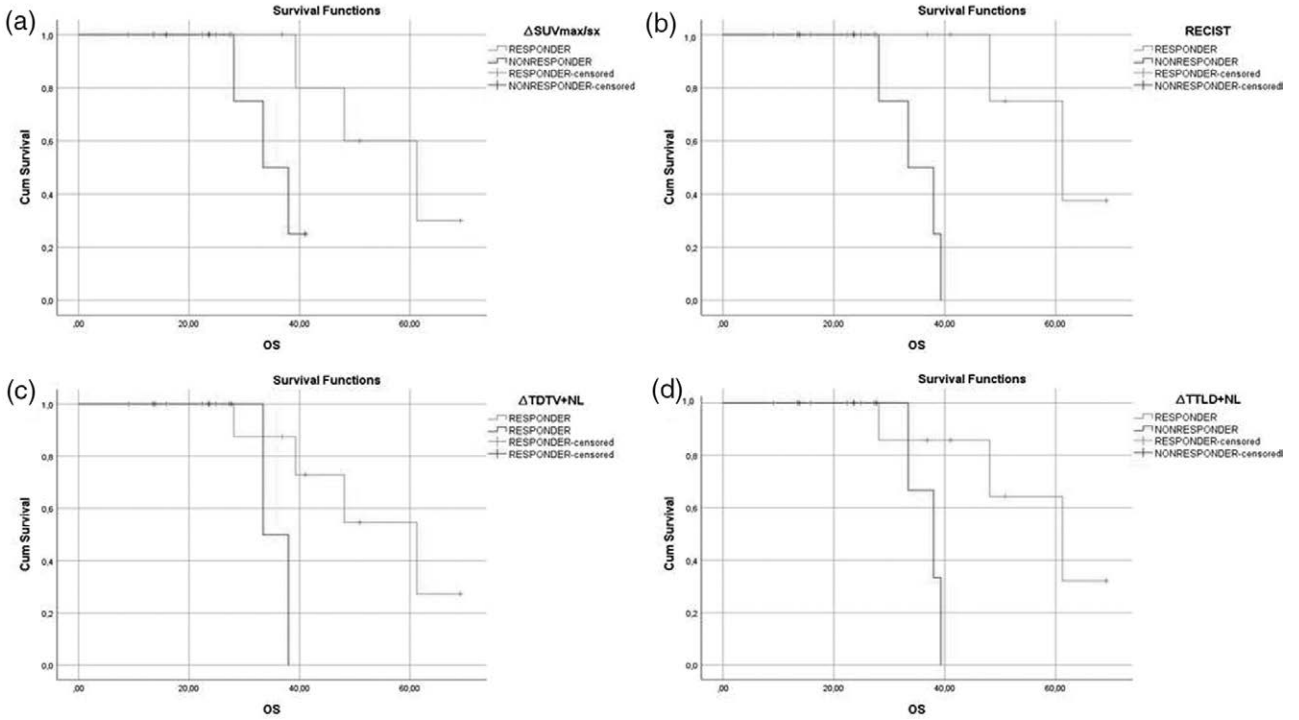
as positive. Semiautomatic volumes of interest were drawn from the primary tumor and metastatic lesions in PET/CT using a 40% SUV threshold in all three planes. SUVmax and SUVmean values of each lesion were recorded. SUVmean/spleenSUVmean (SUVmean/Sm) background values were recorded from the spleen for each patient. In patients whose spleen was operated on, the left renal cortex was used as a background. In addition, the ratio of lesion SUVmax to spleen SUVmax (SUVmax/Sx) was calculated. The DTV value of each lesion was automatically calculated and recorded. TLD values (DTV × SUVmean) of each lesion were calculated and recorded. The highest SUVmax values (HSUVmax), SUVmean (HSUVmean), total DTV (TDTV), and total TLD (TTLD) values were calculated for each patient. In addition, the ratio of TTLD to SUVmean in the spleen (TTLD/Sm) was calculated. SUVmax1, SUVmean1, SUVmax/Sx1, SUVmean/Sm1, DTV1, TLD1, TLD/Sm1 values of each lesion before treatment and SUVmax2, SUVmean2, SUVmax/Sx2, SUVmean/Sm2, DTV2, TLD2, TLD/Sm2 values after treatment were calculated and recorded. Pre-treatment HSUVmax1, HSUVmean1, HSUVmax/Sx1, HSUVmean/Sm1, TDTV1, TTLD1, TTLD/Sm1 and post-treatment HSUVmax2, HSUVmean2, HSUVmax/Sx2, HSUVmean/Sm2, TDTV2, TTLD2, TTLD/Sm2 values were recorded for all patients. For each lesion, SUVmax percent change (ΔSUVmax), ΔSUVmean, ΔDTV, ΔTLD, ΔSUVmax/Sx, ΔSUVmean/Sm, ΔTLD/Sm were calculated. ΔHSUVmax, ΔHSUVmean, ΔTDTV, ΔTTLD, ΔHSUVmax/Sx, ΔHSUVmean/Sm, ΔTTLD/Sm were calculated by adapting the formula below.

ΔMaximum standardized uptake value = (post-treatment maximum standardized uptake value – pre-treatment maximum standardized uptake value)/ pre-treatment maximum standardized uptake value × 100

In the evaluation of molecular response, no lesion showing pathological DOTATATE expression as complete response (CR), independent of the presence of a new lesion and increase of 20% or more in SUV parameters, DTV and TLD as a progressive disease, a decrease of more than 30% as partial response (PR), the group of other than PR and progressive disease was evaluated as stable disease. In addition to the change in both DTV and TLD parameters, a separate grouping was performed in which the presence of a new lesion was considered a progressive disease.

The longest diameter of all primary tumors and metastases and the shortest diameter of lymph nodes were measured in axial sections evaluated with CT. According to the Treatment RECIST 1.1, a total of five target lesions were selected with a maximum of two target lesions in an organ. The disappearance of all target and non-target lesions except lymph nodes with a size (small diameter) < 10 mm was considered as CR, and ≥30% reduction was considered as PR. The presence of a new lesion or an increase in tumor size of more than 20% was considered a progressive disease. Those other than CR, PR, and progressive

Fig. 2



(a) ΔSUVmax/Sx-OS (b) RECIST-OS (c) ΔTDTV + new lesion-OS (d) ΔTTLD + new lesion-OS. Δ, percent change; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; SUVMax/Sx; SUVmax/spleenSUVmax; TDTV, DOTATATE tumor volume; TTLD, total lesion DOTATATE.

Table 4 **Kaplan–Meier and 1- and 3-year survival**

			Estimate survival		Estimate OS at 1 and 3 years	*P* value
	Alive	Exitus	Mean ± SE	Median ± SE		
	N (%)	*N* (%)				
ΔSUVmax/Sx						
Responder	12 (80)	3 (20)	56.59 ± 5.14	61.23 ± 10.45	100 100,	0.034[b]
Nonresponder	3 (50)	3 (50)	35.13 ± 2.44	33.40 ± 4.95	100,50,	
RECIST						
Responder	13 (86.7)	2(13.3)	60.91 ± 4.25	61.23 ± 10.03	100 100	0.002[a]
Nonresponder	2 (33.3)	4 (66.7)	34.70 ± 2.53	33.40 ± 4.95	100,50	
ΔTDTV + new lesion						
Responder	12 (75)	4 (25)	53.65 ± 5.43	61.23 ± 10.48	100,75	0.033[a]
Nonresponder	3 (60)	2 (40)	35.70 ± 2.30	33.40	100,50	
ΔTTLD + new lesion						
Responder	12(80)	3(20)	56.22 ± 5.66	61.23 ± 10.23	100,85	0.030[a]
Nonresponder	3(50)	3(50)	36.90 ± 1.79	38.00 ± 3.75	100,66	
Overall	15(71.4)	6(28.6)	49.79 ± 4.93	48.10 ± 10.73		

Kaplan–Meier test.

Δ, percent change; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; SE, standard error; SUVmax, maximum standardized uptake value; SUVMax/Sx; SUVmax/spleenSUVmax; TDTV, DOTATATE tumor volume; TTLD, total lesion DOTATATE.

[a]Long Rank (Montel–Cox).

[b]Breslow (Generalized Wilcoxon).

disease were considered a stable disease [15]. In all response assessment parameters, CR, PR, and stable disease were considered as responders and progressive disease as nonresponder.

Statistical methods

SPSS version 25.0 (IBM Corporation, Armonk, New York, USA) software was used for statistical analyses. The conformity of univariate data to normal distribution was evaluated with the Shapiro–Wilk test. Mann–Whitney *U* test was used together with Monte Carlo results to compare

Table 5 Multivariate Cox regression analysis for overall survival

						95% CI for Exp(*B*)	
	B	SE	Wald	Sig.	Exp(*B*)	Lower	Upper
ΔTTLD/Sm	0.066	0.082	0.642	0.423	1068	0.909	1255
ΔSUVmax/Sx	−3.395	42 483	0.006	0.936	0.034	0.000	4860
ΔTTLD + new lesion	−28 303	202 189	0.020	0.889	0.000	0.000	6480
ΔTDTV + new lesion	10 937	46 336	0.056	0.813	56 203 000	0.000	1550
RECIST	31 864	201 168	0.025	0.874	68 949 000	0.000	1180

Δ, percent change; CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; SE, standard error; SUVmax, maximum standardized uptake value; SUVMax/Sx; SUVmax/spleenSUVmax; TDTV, DOTATATE tumor volume; TTLD, total lesion DOTATATE.

two independent groups with each other according to quantitative data. Kaplan–Meier (product limit method)-log rank (Mantel–Cox) analysis was used to evaluate the effects of factors on mortality and survival. Cox regression analysis enter method was used to evaluate the effects of prognostic variables on mortality and survival. Quantitative variables were expressed as mean ± SD and median (minimum/maximum), while categorical variables were expressed as *n* (%). All variables were assessed within 95% confidence interval and $P < 0.05$ was considered statistically significant.

Results

Among the 21 patients included in the study, 11 were women, and the mean age of the patients was 58 (44–86). The patients consisted of 7 pancreases, 5 colons, 4 livers, 3 duodena, 1 stomach, and 1 ileum NET, according to their primary tumor localization. Eight patients had been operated on before. A total of 319 metastases were detected including 81 lymph node metastases in 16 patients, 110 liver metastases in 17 patients, 123 bone metastases in 11 patients, and 5 lung metastases in 2 patients. A total of 68 target lesions (2–5) were selected among these lesions. The pre- and post-treatment images of a patient treated with ^{177}Lu-DOTATATE are shown in Fig. 1. Eight of the patients were grade 1, 11 were grade 2, and 2 were grade 3. The histopathological features of the patients, and PET/CT parameters before and after treatment are shown in Table 1.

When ΔTTLD was used to evaluate response to treatment, it was observed that 85.7% of patients (one CR, 10 PR, and seven stable disease) responded to treatment. When RECIST was used to evaluate response to treatment, 71.4% of the patients (one CR, three PR, and 11 stable disease) were found to be responded, and progression was observed in six patients. Response rates and values of other parameters used to evaluate response to treatment are given in Table 2.

In univariate Cox regression analysis, ΔTLD/Sm was found to be statistically significant ($P = 0.044$) on overall survival (OS) (Table 3). When patients were evaluated according to ΔSUVmax/Sx values in Kaplan–Meier survey analysis, 1-year survival was 100% in both responder and nonresponder patients, 3-year survival was 100% in responders and 50% in nonresponders ($P = 0.034$). When evaluated according to RECIST values, 1-year survival was 100% in both responders and nonresponders, and 3-year survival was 100% in responders and 50% in nonresponders ($P = 0.002$). On the basis of ΔTDTV + new lesion values, 1-year survival was 100% in responders and 75% in nonresponders, and 3-year survival was 100% in responders and 50% in nonresponders ($P = 0.033$). According to ΔTTLD + new lesion values, 1-year survival was 100% in responders and 85% in nonresponders, and 3-year survival was 100% in responders and 66% in nonresponders ($P = 0.030$) (Fig. 2, Table 4). No parameter was found as an independent prognostic factor in the multivariant cox regression analysis (Table 5).

Discussion

In this retrospective study, we found that RECIST 1.1 and parameters obtained from ^{68}Ga-DOTATATE PET/CT were prognostic factors on OS in patients treated with ^{177}Lu-DOTATATE.

Because NETs usually progress slowly and are usually diagnosed at an advanced and inoperable stage, treatment options are limited. Treatments with long-acting somatostatin analogs, interferon, or chemotherapy have low response rates [16].

^{177}Lu is a beta and gamma-emitting radionuclide with a maximum tissue penetration range of 2 mm and a half-life of 160 h. ^{177}Lu-DOTATATE is an effective treatment option for patients with well differentiated unresectable or metastatic NET [17]. In the randomized NETTER-1 phase 3 study including patients with progressive midgut neuroendocrine tumors, a 79% lower risk of progression and death was reported with ^{177}Lu-DOTATATE treatment compared to high-dose octreotide long-acting release treatment [4].

Evaluation of response to treatment based on RECIST is widely used in many tumors [18]; however, because NETs are slow-growing tumors that typically show cystic components, RECIST is not an ideal treatment response criterion [19]. It has been reported in some studies that the evaluation of treatment response based on RECIST in slow-growing NETs is not a reliable method [12,20]; however, in the NETTER 1 study [4], RECIST 1.1

criteria were used to evaluate response to treatment. Previous studies have reported that PRRT causes significant measurable changes in tumor size in approximately 30% of patients. Patients with a PR to treatment demonstrate a similar PFS to patients with stable disease [21]. In our study, according to RECIST 1.1, the estimated 1-year survival was 100% in both responders and nonresponders, and 3-year survival was 100% in responders and 50% in nonresponders ($P = 0.002$). The RECIST nonresponder group had the most significant P value on mortality. In most clinical settings, the transition from first-line therapy to second-line therapy occurs by demonstration of morphological progression based on CT or MRI; however, CT or MRI-based response assessment in solid silent tumors often provides limited information, because measurable changes in tumor size require a long time to occur [22]. Therefore, different parameters are needed.

Previous studies have reported that high somatostatin receptor density in PRRT treatment correlates with good treatment response [21]. Haug *et al*. showed that baseline SUVmax was an indicator of response to PRRT [20]. In addition, lower SUVmax values are associated with shorter PFS and OS in patients with NET [23]. Imhof *et al*. reported that a baseline SUVmean value higher than 13.7 was independently associated with a better OS [24]. Several recent studies have reported that higher SUVmax or SUVmean values in baseline ^{68}Ga-DOTA-PET/CT before PRRT treatment are associated with better survival [25–28]; however, it has been reported in different studies that SUV values in basal PET/CT are not a prognostic predictor [29,30]. In our study, we found that pre-treatment SUVmax, SUVmean, and SUV/spleen values did not have statistically significant predictive value on OS.

It is well known that changes in SUVmax of lesions are not always an indicator of response (decreased uptake after treatment may be indicative of a good response, but may also be due to loss of SSTR expression due to tumor dedifferentiation) [9]. In their study, Gabriel *et al*. did not find any correlation between ΔSUVmax and time to progression and therefore concluded that ΔSUVmax is not a useful parameter for the assessment of PRRT response [12]. These data were partially supported by Haug *et al* [20]. In our study, ΔSUVmax and ΔSUVmean values were not found to be predictive values on survival whereas ΔSUVmax/Sx value was found to be statistically significant in predicting mortality.

Zwirtz *et al*. showed that the SUVmax-based assessment of response to treatment was significantly different from that performed with Choi and RECIST 1.1. SUV-based assessment of response to therapy did not correlate with Choi or RECIST 1.1 (P 0.082; $P = 0.496$ and $P = 0.156$; $P = 0.364$) [31]. In the study of Pauwels *et al*., it was reported that DTV higher than 672 ml was associated with worse OS [32]. Tirosh *et al*. found an inverse correlation between DTV with PFS ($P = 0.001$) and disease-specific survival ($P = 0.002$) in their study. DTV higher than 7 ml was associated with a higher probability of progression ($P = 0.04$). DTV values of 35.8 ml or higher were associated with an increased risk of disease-specific death ($P = 0.01$) [11]. In our study, no relationship was found between baseline DTV and TLD with OS; however, when we accept a 20% or more increase in volumetric parameters or the presence of new lesion as progression, which is our treatment response evaluation criteria; according to ΔTDTV + new lesion and ΔTTLD + new lesion values we found statistically significantly lower 1-year and 3-year survival rates in the nonresponder group.

Limitations of our study

The main limitations of our study are that it is a retrospective study and has a limited number of patients. In addition, the inhomogeneity of tumor types was another important limitation. The fact that PFS was not evaluated can be considered another limitation.

Conclusion

In our study, we showed that the parameters SUVmax/Sx, RECIST 1.1, ΔTDTV + new lesion, and ΔTTLD + new lesion which are used in the evaluation of treatment response can predict OS. Our results need to be confirmed by further studies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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