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^{177}Lu-DOTATATE Therapy of Advanced Pancreatic Neuroendocrine Tumors Heavily Pretreated with Chemotherapy: Analysis of Outcome, Safety, and Their Determinants

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Keywords
Pancreatic neuroendocrine tumor · ^{177}Lu-DOTATATE · Peptide receptor radionuclide therapy · Chemotherapy

Abstract
Objective: To retrospectively analyze toxicity, progression-free survival (PFS), overall survival (OS), and their determinants in patients with advanced pancreatic neuroendocrine tumors (PanNETs), previously pretreated with chemotherapy, undergoing peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE. ***Methods:*** A total of 102 patients with advanced PanNETs, previously pretreated with one (67%) or several (33%) lines of chemotherapy, were included, of whom 90% had progressive disease and the majority (74.5%) had grade 2 tumors. ^{177}Lu-DOTATATE, 7.4 GBq per cycle, was administered with 6- to 8-week intervals in 88% of patients utilizing a dosimetry-guided protocol until an absorbed dose of 23 Gy to the kidneys was reached. ***Results:*** A mean dose of 32 ± 10.9 GBq per patient was administered in 1–10 cycles starting a median of 36 months after PanNET diagnosis. The median follow-up was 34 months, the median PFS was 24 months, and the median OS was 42 months from start of PRRT. Independent risk factors for both progression and death were liver tumor burden >50%, more than one line of previous chemotherapy, and elevated alkaline phosphatase. Resection of the primary tumor was linked to longer survival. Bone marrow toxicity grade 3–4 occurred in 10.8%. One patient (1.0%) developed acute myeloid leukemia. Bone marrow toxicity was unrelated to type and length of previous chemotherapy, amount of administered activity, and absorbed dose to the bone marrow. ***Conclusion:*** ^{177}Lu-DOTATATE therapy was feasible, highly effective, and safe in patients with advanced PanNETs heavily pretreated with chemotherapy. More than one line of chemotherapy was a therapy-related independent risk factor for shorter PFS and OS.

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Introduction

According to a growing body of evidence, peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE has emerged as an effective and safe treatment for patients with advanced pancreatic neuroendocrine

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Table 1. Basic patient characteristics (N = 102)

Males	64 (62.7%)
Females	38 (37.3%)
Mean age, years	57.1 (29–79)
Nonfunctional tumor	72 (70.6%)
Functional tumor	30 (29.4%)
PD at baseline	92 (90.2%)
Tumor grade	
Grade 1 (Ki-67 ≤2%)	2 (1.9%)
Grade 2 (Ki-67 3–20%)	76 (74.5%)
Grade 3 (Ki-67 >20%)	7 (6.9%)
NA	17 (16.7%)
Liver metastases	97 (95.1%)
Hepatic tumor burden[a]	
<10%	12 (11.7%)
10–50%	39 (38.2%)
>50%	30 (29.4%)
>50% with liver enlargement	16 (15.7%)
Lymph node metastases	58 (56.8%)
Bone metastases	25 (24.5%)
Pleural and peritoneal metastases	7 (6.7%)
CgA elevated	
Yes	78 (76.5%)
No	22 (21.6%)
NA	2 (1.9%)
ALP >2× UNL	
Yes	26 (25.5%)
No	76 (74.5%)
ECOG performance status	
0	56 (54.9%)
1	40 (39.2%)
2	6 (5.8%)
Uptake on Octreoscan (Krenning scale)	
Grade 3	41 (40.2%)
Grade 4	61 (59.8%)

Values are presented as n (%) or n (range). ALP, alkaline phosphatase; CgA, chromogranin A; ECOG, Eastern Cooperative Oncology Group; NA, not available; PD, progressive disease; UNL, upper normal limit. [a] Percent of total liver volume on CT/MRI.

tumors (PanNETs) [1–5]. Its optimal place and time point in the therapeutic sequence has however not yet been defined. Neither has the ideal treatment protocol been established as regards the number of PRRT cycles, the amount of administered activity and peptide, and the interval between cycles. The original protocol from Rotterdam, whereby 4 cycles of 7.4 GBq ^{177}Lu-DOTATATE are administered with 6- to 8-week intervals, has for example been modified by applying normal tissue (kidney and bone marrow) dosimetry to allow for administering >4 cycles [6, 7]. Since prospective randomized PanNET studies are still lacking, PRRT is in current guidelines positioned as a third or later option in the treatment sequence, preceded by at least one line of chemotherapy [8, 9]. Alkylating chemotherapy before PRRT has been suggested as a potential risk factor for bone marrow toxicity and therapy-related myeloid neoplasms [10–12]. Data on the impact of previous chemotherapy on the outcome of PRRT are however limited. In the present retrospective study on PRRT with ^{177}Lu-DOTATATE, we analyzed progression-free survival (PFS) and overall survival (OS) and their determinants in patients with inoperable, locally advanced, or metastatic PanNETs heavily pretreated with chemotherapy. Further, we assessed safety and factors predisposing to toxicity and adverse effects.

Patients and Methods

Patients

In our hospital's digital patient records, 125 consecutive patients with metastatic and/or locally advanced PanNETs, treated with ^{177}Lu-DOTATATE between November 2005 and November 2014, were identified. A total of 115 patients were pretreated with chemotherapy. Exclusion of 13 patients comprised 8 with missing follow-up, 4 with missing somatostatin receptor scintigraphy (Octreoscan™) who were accepted for PRRT based on ^{68}Ga-DOTATOC-PET/CT, and 1 in whom PRRT was combined with everolimus. The patients' baseline characteristics are shown in Table 1. The study cohort comprised 102 patients: 64 men (62.7%) and 38 women (37.3%), mean age 57.1 years (range 29–79). Seventy-two patients (70.6%) had a nonfunctional tumor, 97 (95.1%) had liver metastases, and 46 (45.1%) had extensive liver tumor burden (>50% of the liver volume). The Ki-67 proliferation index was known in 85 patients; 76 patients (89.4%) had grade 2 (G2) tumors, 7 patients (8.2%) had grade 3 (G3) tumors (all with a Ki-67 index <35%), and 2 patients (2.4%) had grade 1 (G1) tumors. A total of 54 patients (63.5%) had tumors with a Ki-67 index ≤10% and 31 patients (36.5%) with a Ki-67 index >10%. The median time from diagnosis to start of PRRT was 36 months (range 4–254). PRRT was administered because of tumor progression in 92 patients (90.2%), intolerance to other therapies in 8 patients (7.8%), and for the purpose of tumor debulking before surgery in 2 patients (1.9%). Previous therapies are detailed in Table 2. All patients had received one to three lines of various chemotherapy regimens in different sequences (Table 2). Of the 68 patents who received only one line of chemotherapy, the majority (56 patients, 82.3%) were treated with a combination of streptozotocin and 5-fluorouracil (STZ+5FU). Of the 34 patients who received more than one line of chemotherapy, 28 (82.4%) were initially treated with STZ+5FU and subsequently with temozolomide-based therapy, which in 21 patients was administered as monotherapy and in 7 in combination with capecitabine (TEM+CAP). The remaining 6 patients received

Table 2. Patient characteristics – treatments before PRRT

Surgery total	43 (42.2%)
Surgery primary tumor	38 (37.3%)
Liver surgery	7 (6.9%)
Chemotherapy	102 (100%)
STZ+5FU	87 (85.3%)
TEM	28 (27.5%)
TEM+CAP	17 (16.7%)
Platinum-based	13 (12.7%)
Lines of chemotherapy	
One line	68 (66.7%)
STZ+5FU	56 (82.3%)
TEM+CAP	6 (8.8%)
Platinum-based	4 (5.9%)
TEM	2 (2.9%)
Two lines	29 (28.4%)
Three lines	5 (4.9%)
Targeted therapies (everolimus, sunitinib)	16 (15.7%)
Biotherapy	62 (60.8%)
Somatostatin analog	58 (56.9%)
Interferon	24 (23.5%)
Liver embolization	11 (10.8%)
Particle embolization	9 (8.8%)
Chemoembolization	2 (1.9%)
Radiofrequency ablation	17 (16.7%)
Radiotherapy	4 (3.9%)

Values are presented as *n* (%). 5FU, 5-fluorouracil; CAP, capecitabine; PRRT, peptide receptor radionuclide therapy; STZ, streptozotocin; TEM, temozolomide.

other treatment regimens as first and second line treatments. The median duration of treatment with alkylating agents was 13 months (range 2–144).

PRRT with ^{177}Lu-DOTATATE

The inclusion criteria for PRRT at our department have previously been detailed [6] and were briefly tumor somatostatin receptor expression higher than that in the normal liver (Krenning score 3 and 4) on somatostatin receptor scintigraphy as well as sufficient hematological status and liver and kidney function. Chemotherapy and targeted therapy were stopped at least 1 month before PRRT. Long-acting somatostatin analogs were administered until latest 2 weeks before PRRT and short-acting analogs were stopped at least 12 h before treatment start. Patients with functional tumors continued with somatostatin treatment during therapy. PRRT was performed according to previously published procedures [6] whereby 7.4 GBq ^{177}Lu-DOTATATE was administered with 6- to 8-week intended intervals between cycles. The peptide was a kind gift from Prof. Eric Krenning, ^{177}Lu was purchased (IDB, Holland BV), and labeling was performed in-house. Kidney protection comprised 2 L i.v. amino acid mixture (Vamin 14 gN/L electrolyte-free; Fresenius Kabi) given as an 8-h infusion starting 0.5 h before PRRT. Antiemetics (5-HT_3 blocker and 8 mg of betamethasone) were injected i.v. 1 h before therapy. Before every treatment cycle, white blood cells had to be $>3 \times 10^9$/L, granulocytes $>1.5 \times 10^9$/L, and platelets $>100 \times 10^9$/L. PRRT was terminated if these criteria were not met within 6 months. In some cases, the administered activity per cycle was decreased by 30% rather than delaying the treatment. The first 12 patients were treated according to the Rotterdam standard 4-cycle protocol, and all subsequent 90 patients (88.2%) underwent PRRT according to a dosimetry-guided protocol (EduraCT nr 2009-012260-14) [6, 13, 14], whereby as many cycles as possible were administered until 23 Gy absorbed dose to the kidneys or 2 Gy to bone marrow was reached, or other reasons to stop therapy occurred. In 12 (11.8%) patients with favorable tumor response, salvage therapy aiming at 40 Gy accumulated absorbed dose to the kidneys was offered upon progression.

Follow-Up and Data Collection

The median follow-up time was 34 months (range 4–160). Medical and radiological reports were retrospectively evaluated. For Swedish patients (46.1%) survival data were derived from the National Health Registry until March 2018. The referring sites supplied all other available follow-up data. All patients had at least 12 months of follow-up from therapy start unless earlier progression or death occurred. PFS was calculated from start of therapy to date of radiologically confirmed progression (RECIST 1.1) or death from any cause. In 3 patients date of progression was based on scintigraphic findings, and in 1 subject progressive disease (PD) was diagnosed based on increasing tumor markers and subsequently confirmed by CT. OS was calculated from the first day of treatment until the day of death or until the last day of follow-up.

Response and Toxicity Evaluation

Intravenous contrast-enhanced CT/MRI was performed, according to clinical NET imaging protocols, at baseline within 1 month before the start of PRRT, before every second treatment cycle, 3 months after the last treatment, and at least every 6 months thereafter until documented disease progression according to RECIST 1.1. Hepatic tumor burden was assessed on baseline CT/MRI (percent tumor of liver volume) and the total tumor burden was estimated on whole body scans obtained 24 h after the first PRRT cycle. Thus, for all types of metastases (liver, lymph nodes, bone, peritoneal, pleural), grading of the disease extent was performed according to arbitrary scales as follows: liver metastases 1–4 (limited, <50% of liver volume, >50% of liver volume, and extensive metastases with liver enlargement), bone metastases 1–3 (occasional metastases, moderate extent, and extensive metastases), lymph nodes 1–3 (occasional regional, multiple regional, and multiple on both sides of diaphragm), peritoneal and/or pleural metastases 1–2 (occasional and several metastases). Tumor burden was assessed as a sum of points for all types of metastases. Kidney, liver, and bone marrow toxicity was recorded according to the WHO criteria (CTCAE v3.0) [15]. In patients with elevated plasma chromogranin A (CgA) and/or other hormones, a 50% decrease or a normalization of these values was considered as biochemical response.

Statistical Methods

Statistical analyses utilized SAS software version 9.4 (SAS Institute, Cary, NC, USA) and R (version 3.2.2). OS and PFS were calculated with the Kaplan-Meier method. Selected baseline factors

Table 3. Significant predictors of PFS and OS

Variable	*n*	PFS (95% CI) in months	Univariate analysis, *p* value	Multivariate analysis		OS (95% CI) in months	Univariate analysis, *p* value	Multivariate analysis	
				HR (95% CI)	*p* value			HR (95% CI)	*p* value
Age	102								
≤65 years		23 (17–30)	0.909			41 (29–70)	0.438		
>65 years		27 (12–37)				40 (24–74)			
ECOG status	102								
0		31 (24–36)	0.001			74 (41–)	<0.001	2.38 (1.39–4.08)	0.002
≥1		14 (10–18)				25 (15–39)			
Functionality	102								
Nonfunctional		28 (18–31)	0.988			43 (31–70)	0.566		
Functional		18 (14–27)				32 (21–61)			
PD at baseline	102								
No		50 (4–)	0.003			97 (11–)	0.158		
Yes		23 (17–28)				39 (29–58)			
Ki-67	85								
≤10%		28 (18–34)	0.131			41 (29–79)	0.278		
>10%		16 (11–27)				26 (16–70)			
Uptake on Octreoscan	102								
Grade 3		28 (17–37)	0.132			53 (29–110)	0.172		
Grade 4		24 (16–28)				32 (26–61)			
Hepatic tumor burden[a]	97								
≤50%		35 (24–43)	<0.0001	1.86 (1.15–3.00)	0.012	79 (43–142)	<0.0001	2.38 (1.34–4.22)	0.003
>50%		16 (9–18)				23 (14–31)			
Bone metastases	102								
No		28 (20–35)	0.0007	2.14 (1.28–3.57)	0.004	53 (32–79)	0.004		
Yes		14 (8–18)				25 (11–42)			
Surgery primary	102								
No		18 (14–26)	0.013			29 (23–41)	0.003	0.54 (0.30–0.96)	0.037
Yes		35 (20–42)				84 (42–)			
Chemotherapy	102								
One line		28 (23–35)	0.002	2.12 (1.32–3.41)	0.002	61 (32–110)	0.004	2.33 (1.38–3.94)	0.002
More than one line		14 (11–20)				26 (21–40)			
CgA > UNL	100								
No		46 (31–)	0.0002	2.79 (1.38–5.61)	0.004	110 (61–)	0.005		
Yes		18 (14–27)				32 (24–42)			
CgA > 10× UNL	100								
No		31 (24–37)	0.002			70 (41–110)	0.0003		
Yes		14 (9–23)				20 (12–32)			
ALP >2× UNL	102								
No		30 (23–35)	0.0001	2.17 (1.26–3.71)	0.005	61 (39–110)	<0.0001	2.76 (1.54–4.94)	0.0007
Yes		12 (9–17)				23 (11–29)			

ALP, alkaline phosphatase; CgA, chromogranin A; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; UNL, upper normal limit. [a] Percent of total liver volume on CT/MRI.

were tested in univariate analysis (Table 3). Variables showing a trend for an effect in the univariate analysis ($p < 0.1$) were further analyzed in a multivariate analysis (Cox proportional hazards model). Only significant risk factors were presented with hazard ratio, 95% confidence interval, and *p* value. Statistical significance was defined as a *p* value <0.05. Since the number of patients in the G1 and G3 groups was limited and did not allow for subgroup analysis, we chose the Ki-67 index with a 10% cutoff as a potential predictor. The influence of different factors on development of bone marrow toxicity was assessed using uni- and multivariate logistic regression models. Categorical variables were presented as frequency values and comparisons utilized Pearson's χ^2 test (or, if applicable, Fisher's exact test).

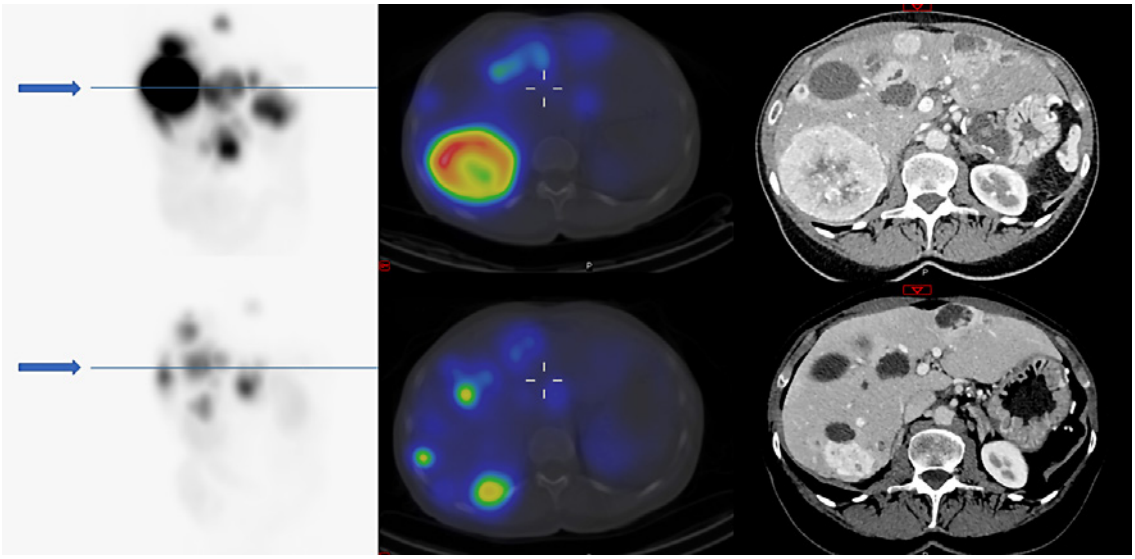

Fig. 1. ^{177}Lu-DOTATATE therapy images in a patient with G2 PanNET who achieved PR. From left to right: maximum intensity projection, fused SPECT/CT, and contrast-enhanced CT at first (upper row) and last (sixth) treatment cycle (lower row). A distinct shrinkage of the liver metastases in the right lobe with a high absorbed tumor dose is illustrated. G2, grade 2; PanNET, pancreatic neuroendocrine tumor; PR, partial response.

Results

Peptide Receptor Radionuclide Therapy

A mean of 32 ± 10.9 GBq (range 7.4–74) were administered in a median of 4 (range 1–10) cycles; 44 patients (43.1%) received >4 cycles. In 51 patients (50%), 23 Gy absorbed dose to the kidneys was reached after 3–10 cycles. Other reasons to terminate the treatment were progression in 17 patients (16.7%), bone marrow toxicity in 11 patients (10.8%), application of a standard PRRT protocol of 4 cycles in 9 patients (8.8%), combination of factors in 7 patients (6.8%), decrease of tumor load in 3 patients (2.9%), general deterioration in 2 patients (1.9%), and death in 2 patients (1.9%). The cumulative absorbed dose to the bone marrow did not reach 2 Gy in any patient.

Toxicity

Bone marrow toxicity grade 3 or 4 occurred in 11 patients (10.8%). Bone marrow toxicity was the only reason or one of the reasons for stopping PRRT in 18 patients (17.6%). Grade 3 toxicity of white blood cells and/or granulocytes occurred in 5 patients (4.9%), grade 3 toxicity of hemoglobin occurred in 2 patients (1.9%), and grade 3 or 4 toxicity of platelets occurred in 5 patients (4.9%). One patient developed lethal grade 4 thrombocytopenia, and 1 patient (1.0%) developed acute myeloid leukemia 48 months after PRRT start. The latter patient was a 61-year-old woman who had received 8 cycles of STZ+5FU and underwent primary tumor resection before PRRT, administered as 6 cycles (44 GBq), and for whom no grade 3 or 4 bone marrow toxicity was observed during the treatment and follow-up. In one patient with large hepatic tumor load who developed fatal liver toxicity 6 weeks after receiving the second PRRT cycle, tumor progression was also considered as a cause of death. Development of bone marrow toxicity (toxicity above grade 2 or the necessity to finish the treatment because of bone marrow toxicity) was unrelated to patient-related parameters (sex, age, extent of liver metastases and presence of bone metastases, type and length of previous chemotherapy) and to PRRT parameters (administered activity, number of cycles, and bone marrow dose). No grade 3 or 4 nephrotoxicity was observed.

Tumor Response

RECIST 1.1 assessment was performed in 100 patients; 2 patients died before CT/MRI evaluation. The best morphological response was complete response (CR) in 4 patients (4%), partial response (PR) in 45 patients (45%), stable disease (SD) in 44 patients (44%), and PD in 7 patients (7%). Objective response (CR+PR) was reached in 49%. The median time to best response was 14.8 months (range 3–108). In the subgroup of 92 patients with PD at

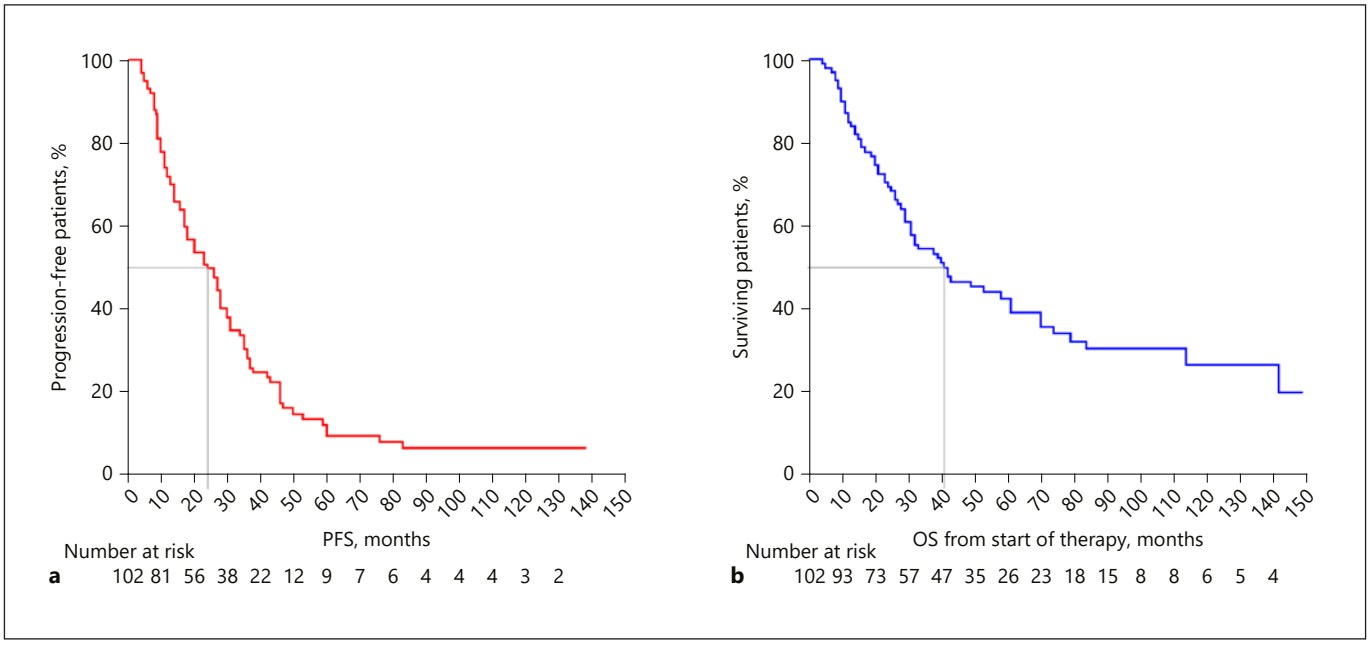

Fig. 2. PFS (**a**) and OS (**b**) from the start of PRRT with ^{177}Lu-DOTATATE. OS, overall survival; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy.

the start of PRRT and known morphological response, disease control (CR+PR+SD) was achieved in 91.0%. Figure 1 shows tumor response in a patient with a G2 PanNET with liver and bone metastases.

PFS and OS

The median PFS was 24 months (95% CI 17–28) and OS was 42 months (95% CI 29–61) (Fig. 2). The median survival from diagnosis was 88 months (95% CI 70–153). A total of 63 patients (61.8%) died during follow-up. Tumor progression was the cause of death in 60 patients (95.2%). In 2 patients who died due to thrombocytopenia and liver failure, respectively, PRRT may have been a contributing factor for death. One patient died of unknown reasons. Significant predictors of PFS and OS in uni- and multivariate analysis are presented in Table 3. Extended liver metastases (liver tumor burden >50%), more than one line of chemotherapy, and elevated alkaline phosphatase >2× the upper normal limit were independent risk factors for both progression and death (Table 3). Presence of bone metastases and elevated CgA levels were linked to shorter PFS. Surgery of the primary tumor and Eastern Cooperative Oncology Group status 0 were independent positive prognostic factors for OS (Table 3). Figure 3 presents PFS and OS in relation to liver tumor load and Figure 4 in relation to number of lines of chemotherapy. A separate comparison of patients having received one versus more than one line of chemotherapy was performed in order to exclude other factors that could explain the different outcome in these two groups (Table 4). All the parameters in the patients' baseline characteristics at start of PRRT were the same, and the time interval from diagnosis to start of PRRT was similar in these two groups.

Patients with morphological response (CR+PR) had both longer PFS and OS than those with SD (log-rank test $p = 0.002$, 31 vs. 17 months median PFS, and log-rank test $p = 0.001$, 70 vs. 31 months median OS) (Fig. 5).

Biochemical Response

CgA levels were available in 100 patients (98%) and were elevated at the start of PRRT in 78 patients (78%). CgA decreased >50% or was normalized in 52% of patients. A decrease >50% or normalization was associated with longer PFS (log-rank test $p = 0.003$, 28 vs. 14 months) and with longer OS (log-rank test $p = 0.0001$, 70 vs. 21 months). Hormone levels were elevated in all patients with functional tumors (29%) at therapy start. A decrease of hormone levels >50% occurred in 68% of patients and was associated with longer PFS (log-rank test $p = 0.006$, 27 vs. 16 months) and OS (log-rank test $p = 0.008$, 58 vs. 28 months).

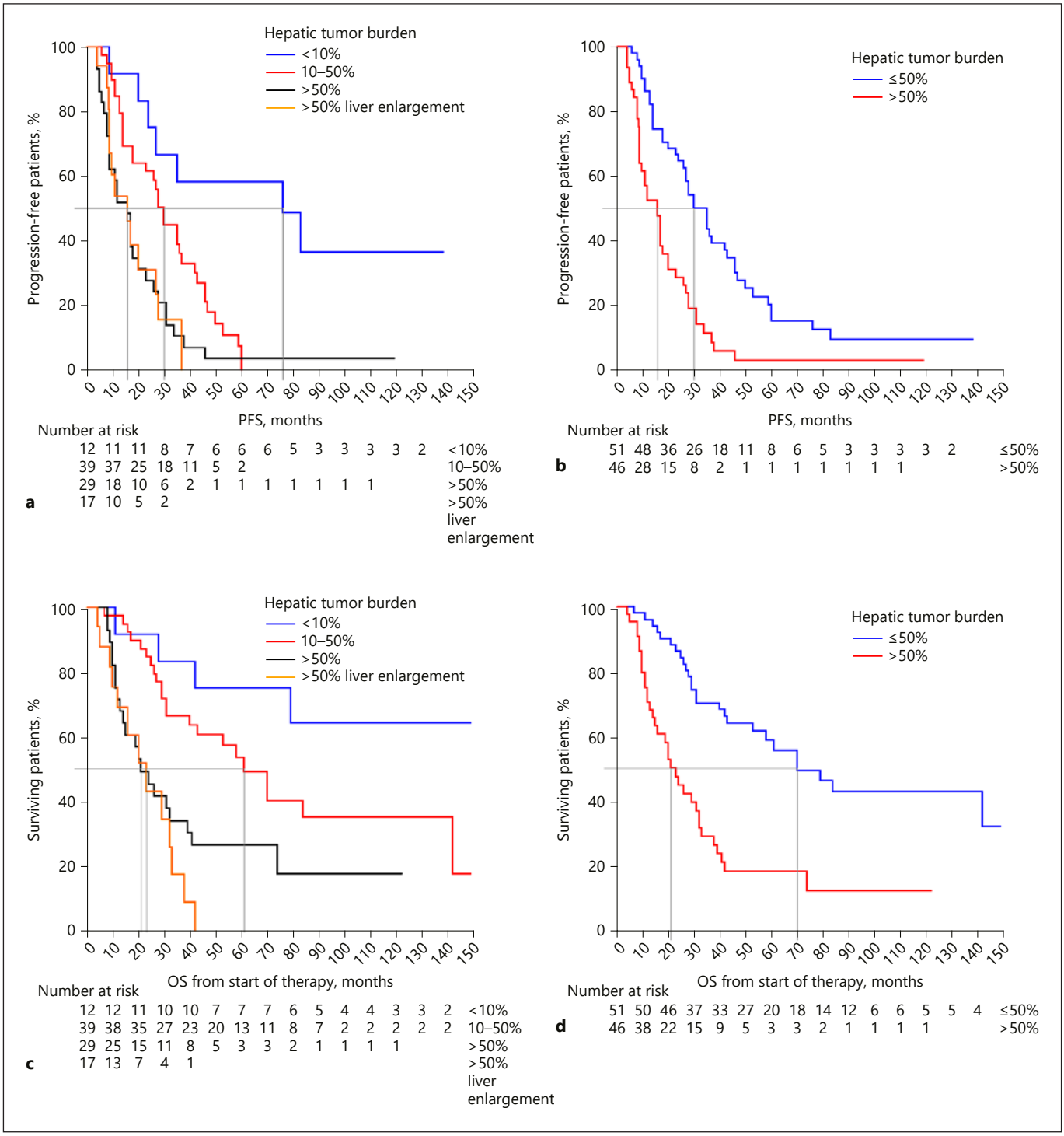

Fig. 3. PFS (**a**, **b**) and OS (**c**, **d**) in relation to liver tumor load. Study population divided into four groups (**a**, **c**) and two groups (**b**, **d**) according to liver tumor load. OS, overall survival; PFS, progression-free survival.

Table 4. Comparison of subgroups of patients having received one versus more than one line of chemotherapy

Variable	One line of CTx (n = 68)	Several lines of CTx (n = 34)	Total	p value
Age				
≤65 years	53 (77.9%)	26 (76.5%)	79 (77.5%)	0.867
>65 years	15 (22.1%)	8 (23.5%)	23 (22.5%)	
ECOG status				
0	40 (58.8%)	16 (47.1%)	56 (54.9%)	0.260
≥1	28 (41.2%)	18 (52.9%)	46 (45.1%)	
Functionality				
Nonfunctional	48 (70.6%)	24 (70.6%)	72 (70.6%)	1.000
Functional	20 (29.4%)	10 (29.4%)	30 (29.4%)	
PD at baseline				
No	8 (11.8%)	2 (5.9%)	10 (9.8%)	0.346
Yes	60 (88.2%)	32 (94.1%)	92 (90.2%)	
Time to start of PRRT				
Mean (standard deviation)	49.8 (51.5)	58.0 (50.2)	52.5 (51.0)	0.083
Median (min, max)	28.6 (4, 254)	44.1 (9, 227)	35.9 (4, 254)	
Q1, Q3	14.9, 68.8	26.8, 58.2	17.5, 65.9	
Uptake on Octreoscan				
Grade 3	29 (42.6%)	12 (35.3%)	41 (40.2%)	0.475
Grade 4	39 (57.4%)	22 (64.7%)	61 (59.8%)	
Surgery of the primary tumor				
No	41 (60.3%)	23 (67.6%)	64 (62.7%)	0.469
Yes	27 (39.7%)	11 (32.4%)	38 (37.3%)	
Ki-67≤10%				
Yes	37 (64.9%)	17 (60.7%)	54 (63.5%)	0.752
No	20 (35.1%)	11 (39.3%)	31 (36.5%)	
Hepatic tumor burden[a]				
≤50%	36 (56.3%)	15 (45.5%)	51 (52.6%)	0.313
>50%	28 (43.8%)	18 (54.5%)	46 (47.4%)	
Bone metastases[b]				
No	54 (79.4%)	23 (67.6%)	77 (75.5%)	0.193
Yes	14 (20.6%)	11 (32.4%)	25 (24.5%)	
Total tumor burden[b]				
Median (min, max)	4.00 (1.0, 9.0)	5.00 (2.0, 11.0)	5.00 (1.0, 11.0)	0.106
Q1, Q3	3.00, 6.00	4.00, 6.00	3.00, 6.00	
Elevated CgA				
No	17 (25.8%)	5 (14.7%)	22 (22.0%)	0.206
Yes	49 (74.2%)	29 (85.3%)	78 (78.0%)	
CgA >10× UNL				
No	44 (66.7%)	20 (58.8%)	64 (64.0%)	0.439
Yes	22 (33.3%)	14 (41.2%)	36 (36.0%)	
ALP >2× UNL				
No	53 (77.9%)	23 (67.6%)	76 (74.5%)	0.261
Yes	15 (22.1%)	11 (32.4%)	26 (25.5%)	

ALP, alkaline phosphatase; CgA, chromogranin A; CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; Q1, first quartile; Q3, third quartile; UNL, upper normal limit. [a] Percent of total liver volume on CT/MRI. [b] Estimated on whole body scans obtained 24 h after the first PRRT cycle.

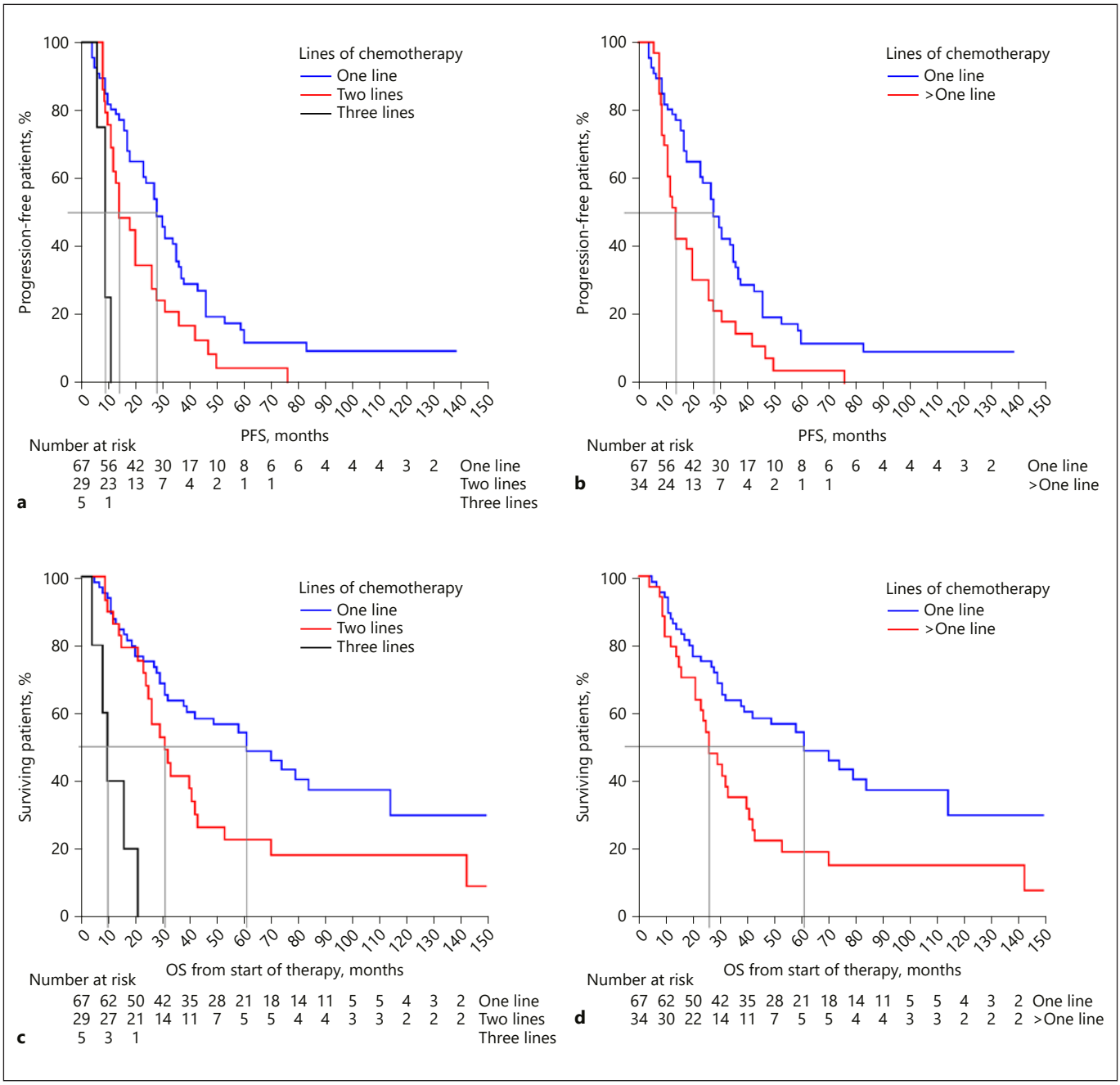

Fig. 4. PFS (**a**, **b**) and OS (**c**, **d**) in relation to number of lines of chemotherapy. Study population divided into three groups (**a**, **c**) and two groups (**b**, **d**). OS, overall survival; PFS, progression-free survival.

Discussion

In this study, we found PRRT with ^{177}Lu-DOTATATE to be effective and safe, also in PanNET patients heavily pretreated with chemotherapy. Several lines of previous chemotherapy was identified as one of the independent factors which impaired the long-term outcome. Even though our patients had previously received alkylating chemotherapy, notably the bone marrow toxicity was comparable to that reported for PRRT trials in which patients were pretreated with chemotherapy to a much lesser extent [2–5] (Table 5). The bone marrow toxicity in our patients was found to be unrelated to the type and length

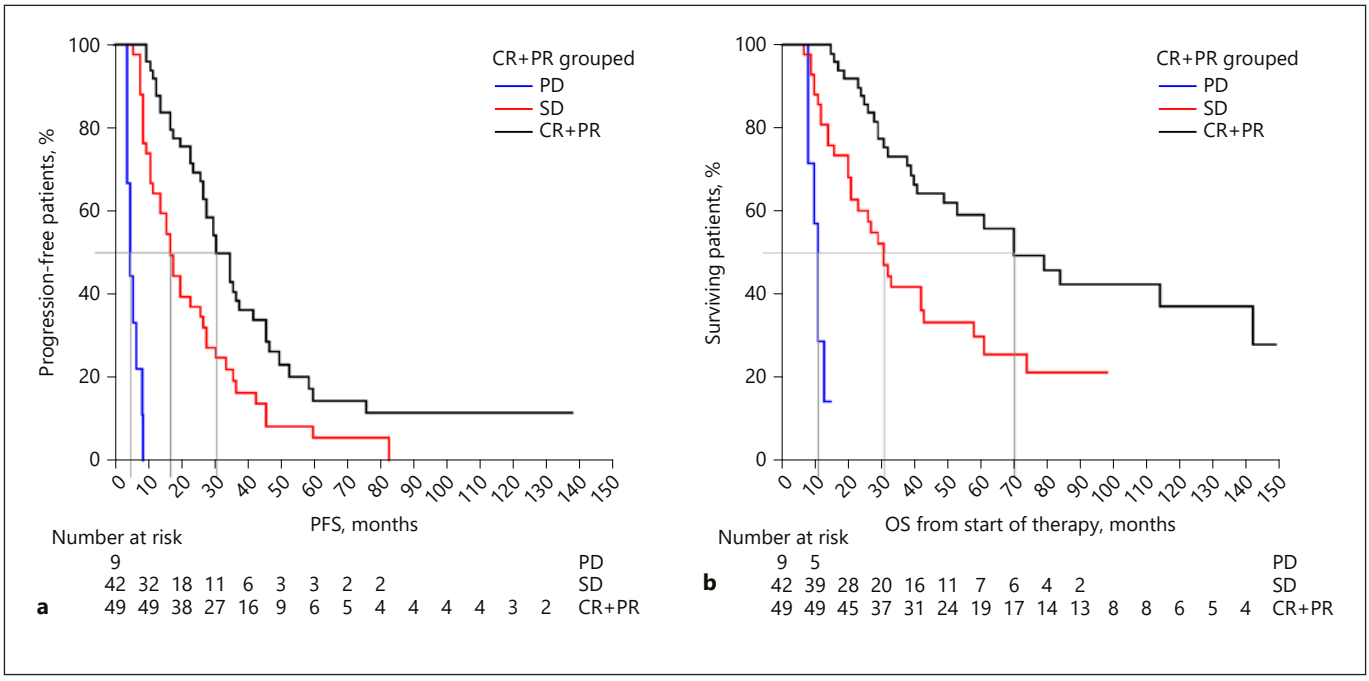

Fig. 5. PFS (**a**) and OS (**b**) in relation to morphological response: CR+PR (black line), SD (red line), and PD (blue line). CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

of chemotherapy and to the administered amount of ^{177}Lu-DOTATATE activity. In agreement with earlier reports, bone marrow dose was not a useful predictor for bone marrow toxicity [6, 11]. In previous studies including a large number of patients, prior chemotherapy with alkylating agents was associated with a higher incidence of bone marrow toxicity and therapy-related myeloid neoplasms [10–12]. Surprisingly, we could not show any increased incidence of therapy-related myeloid neoplasms in our patients who received higher than the standard total administered ^{177}Lu-DOTATATE activity and in addition were heavily pretreated with chemotherapy. The median 34 months of follow-up may, however, have been too short to detect all occurrences of therapy-related myeloid neoplasms.

All available evidence for PanNET treatment outcomes with PRRT was recently presented by Ramage et al. [16]. For comparison of our results with those of others, we selected only studies in well-defined cohorts of PanNET patients as regards treatment protocols and patient characteristics, such as tumor grade, tumor load, and number and types of previous treatments [2–5] (Table 5). Both PFS (median 24 months) and OS (median 42 months) in our patients were shorter than those reported in other studies, which, however, must be related to the different patient selection [2–5] (Table 5). In our cohort, patients were heavily pretreated with chemotherapy and had longer time from diagnosis to start of PRRT. The other studies [2–5] included a larger fraction of patients with G1 tumors, who generally have better prognosis. In the study by Brabander et al. [4], including the largest cohort of PanNET patients so far, only patients who received at least 22.2 GBq of ^{177}Lu-DOTATATE were included for evaluation of efficacy (Table 5). Interestingly, a subgroup analysis in those of our patients who had received the same activity (92 patients) resulted in similar PFS (median 27 vs. 30 months), but still clearly shorter OS (median 43 vs. 71 months).

In patients with advanced PanNETs there are several available systemic treatments, including biotherapy, chemotherapy, targeted molecular therapies, and PRRT. There is long-standing experience using the combination of STZ+5FU with reported response rates of up to 39% (RECIST) [17, 18] and a median PFS ranging from 9.3 [18] to 23 months [19]. TEM+CAP has in several nonrandomized trials shown a response rate of up to 70% and a median PFS of 11–18 months [20, 21]. The evidence for TEM alone is rather limited. One study reported a radiological response rate of 14% and a median PFS of 7 months [22]. The first randomized study with TEM+CAP versus

Table 5. Comparison of studies with ^{177}Lu-DOTATATE in patients with PanNETs

	Ezziddin et al. [2]	Sansovini et al. [3]	Brabander et al. [4]	Demirci et al. [5]	Present study
Type of study	retrospective	phase 2	retrospective	retrospective	retrospective
Patients with PanNETs, *n*	68	60	443 NETs (133 PanNETs)	186 NETs (68 PanNETs)	102
Administered activity	8.0 GBq ×4	5.5 GBq ×5 or 3.7 GBq ×5 (total activity 18.5 or 27.8 GBq)	7.4 GBq ×4 (at least 22.2 GBq)	5.0 GBq (3.7–8.1) in 6 (3–12) cycles	7.4 GBq (1–10 cycles, mean total activity 32 GBq)
Liver metastases, %	97.1	80	78[a]	75.3[a]	95.1
Bone metastases, %	32.3	NA	16[a]	41.4[a]	24.5
PD at start, %	67.6	100	54[a]	80.6[a]	90.2
Previous chemotherapy, %	25	25	6[a]	33.3[a]	100
Grade 1, %	27.9	26.7	38[a]	30.7[a]	2.4
Grade 2, %	72.1	53.3	57[a]	54.3[a]	89.4
Grade 3, %	0	0	5[a]	15[a]	8.2
Median time from diagnosis to start of PRRT, months	NA	NA	14[a]	19[a]	36
Outcome					
Response criteria, %	RECIST 1.1	SWOG	RECIST 1.1	RECIST 1.1	RECIST 1.1
CR	0	6.6	5	4.8	4
PR	57.4	23.3	50	56.5	45
SD	27.9	51.7	30	8.1	44
PD	14.7	18.3	13	30.6	7
DCR	85.3	81.7	85	69.4	91
ORR	57.4	29.9	55	61.3	49
Median OS, months	53	NR	71	57 (mean)	42
Median PFS, months	34	29	30	42 (mean)	24
Median follow-up, months	58	59	78	30	34
Side effects					
Bone marrow malignancy, %	0	0	1.5 MDS, 0.7 AL	0	1.0 AML
Hematotoxicity grade 3/4, %	5.9	0	10	1.5	10.8
Kidney toxicity grade 3/4, %	0	0	0	0	0
Liver toxicity, %	0	0	0	0	1.0

AL, acute leukemia; AML, acute myeloid leukemia; CR, complete response; DCR, disease control rate; MDS, myelodysplastic syndrome; NA, not available; NET, neuroendocrine tumor; NR, not reached; ORR, overall response rate; OS, overall survival; PanNET, pancreatic neuroendocrine tumor; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SWOG, Southwest Oncology Group.
[a] Calculated in the whole group of patients with mixed NET types.

TEM alone showed longer median PFS (22.7 vs. 14.4 months) and higher rates of adverse effects in the combination arm [23]. Targeted molecular therapies with everolimus and sunitinib in well-differentiated G1–G2 PanNETs have shown a median PFS of 11 and 11.4 months [24, 25]. Long-term outcomes obtained with PRRT in patients with PanNETs have in several retrospective studies compared favorably with those achieved with chemotherapy and targeted agents [1–5]. PRRT is also an effective cytoreductive therapy with an overall response rate of 30–61% in the literature [1–5] and 49% in our study. Pozzari et al. [26] reviewed the cytoreductive potential of different systemic treatments, including only studies where tumor shrinkage was reported with a waterfall plot and tumor downsizing ≥10% was considered as objective response. Using the same criteria on our data,

we obtained tumor shrinkage in 75% of our patients, which places PRRT besides TEM+CAP among the treatments with the highest cytoreductive potential, with only PRRT combined with TEM+CAP being more effective. Because of the lack of prospective randomized controlled trials, in current guidelines for G1/G2 PanNETs, PRRT is recommended as a second-line alternative to TEM+CAP after failure of somatostatin analogs (in selected patients) and at least one line of chemotherapy (STZ+5FU) and/or targeted therapy [8, 9].

There are only limited data on how previous chemotherapy impacts the outcome of PRRT. In 51 patients with mixed NET types, including 14 PanNETs, previous chemotherapy was found to be a negative predictive factor for OS [27], but in the German multi-institutional registry study in 450 patients, including 185 with PanNETs, the number of previous therapies, including chemotherapy, did not influence either PFS or OS [28]. Our study is the first to show that ^{177}Lu-DOTATATE therapy in patients having undergone more than one line of chemotherapy results in considerably shorter PFS and OS than in those with only one line of previous cytostatic treatment (median PFS 14 vs. 28 months and median OS 26 vs. 61 months). Subgroup analysis showed that the two groups at therapy start were similar considering time to start of PRRT, morbidity status, disease progression, tumor grade, surgery of the primary tumor, tumor burden, and somatostatin receptor expression. We are aware of the fact that the choice of treatment sequence in PanNETs for the individual patient is based on a number of different factors. There is therefore a risk for possible selection bias with more lines of chemotherapy administered to patients with more aggressive disease. The choice of administering two lines of chemotherapy before PRRT was however in the majority of our patients not solely based on tumor-related factors, but rather on our local routines and the availability of PRRT at that time.

TEM alone or TEM+CAP was routinely applied as second-line treatment in our center before PRRT became available and before we had gained sufficient experience with the therapy. Further, in foreign patients the treatment sequence was decided at the referring center were PRRT was not available. From both preclinical and clinical studies, alkylating agents are known to promote somatic mutations. Interestingly, although limited to three patients, Raj et al. [29] in their study found clonal evolution patterns contributing to malignant tumor transformation in PanNETs using next-generation sequencing in samples before and after chemotherapy. The results of our study, despite its retrospective and nonrandomized design, nevertheless indicate that PRRT is probably better suited earlier in the treatment sequence, no later than after one line of chemotherapy (STZ+5FU). In patients with low-grade PanNETs, long expected survival, and a likelihood to benefit from PRRT, the exposure to several lines of alkylating agents can compromise both safety and efficacy of this treatment in the future. Contrary to chemotherapy, PRRT can be administered as salvage treatment after later progression after successful result of the first treatment [30].

Apart from several lines of previous chemotherapy, the independent risk factors influencing PFS and OS were linked to tumor load and general performance status. Extended liver metastasis and presence of bone metastases are both factors known to impair the outcome of PRRT [1, 2, 4, 5]. A cutoff value of >50% of the liver replaced by metastasis was, in our study, found the best predictive separator for shorter PFS and OS. In line with previous reports, normal baseline CgA was identified as a favorable predictive factor for PFS in our patients [31, 32], indicating that patients with low tumor load are likely to respond better to the treatment. Indeed, all patients who achieved CR in our study had low tumor load and normal baseline CgA. Surprisingly, proliferation rate, expressed as Ki-67 index with a 10% cutoff, was not a significant predictor for either PFS or OS in our patients predominantly harboring G2 tumors.

The response rates with PRRT are generally higher for PanNETs than for small intestinal neuroendocrine tumors [6, 1, 33]. Ilan et al. [34] demonstrated a correlation between the absorbed dose in PanNET metastases and tumor shrinkage, whereas this dose-response relationship could not be established for small intestinal NETs [35]. PanNETs may therefore benefit from administering PRRT with higher amounts of activity, although without exceeding the maximum tolerated absorbed dose to risk organs (kidneys and bone marrow) [3]. Accordingly, a PFS and OS benefit was shown in a prospective trial encompassing 200 NET patients (49 PanNETs) for those who received the maximum number of cycles compared to those who did not [6]. Further, the morphological response in our patients was clearly related to both PFS and OS. These findings indicate that PanNET patients may benefit from a dosimetry-guided protocol and warrants further evaluation in prospective studies.

The median OS from diagnosis in our patients was 88 months. For matters of comparison, we also performed a subgroup analysis in patients with documented TNM stage IV at diagnosis (93%), for whom the median OS from diagnosis was 85 months and with a 5-year surviv-

al of 65% and a 10-year survival of 40%. These results compared favorably with the SEER data, showing a median OS of 60 months [36] for patients with metastasized G1 and G2 PanNET diagnosed between 2000 and 2012. We have also observed a survival benefit, compared with historical survival data, in advanced PanNET patients treated in our center before the era of PRRT with a median OS from diagnosis of 56 months [37, 38]. We assume that this longer survival can at least partly be attributed to PRRT.

This study has several limitations. The study design was retrospective and nonrandomized and with a risk for selection bias regarding the place for PRRT vis-à-vis chemotherapy in the treatment sequence.

Conclusion

^{177}Lu-DOTATATE therapy was feasible and highly effective, with a median PFS of 24 months and a median OS of 42 months, in patients with advanced, inoperable PanNETs heavily pretreated with chemotherapy. More than one line of chemotherapy constituted a therapy-related independent risk factor for shorter PFS and OS. Patients with morphological response achieved PFS and OS benefits. Dosimetry-based therapy was feasible and patients receiving the number of cycles required to reach 23 Gy absorbed dose to the kidneys achieved better morphological response than those who did not.

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Statement of Ethics

All procedures performed in this study were in accordance with the ethical standards of the National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A total of 48 patients included in a previous prospective study (EudraCT nr 2009-012260-14) were enrolled according to local ethics committee approval (No. 2009-320) after providing written informed consent [6]. For the remaining patients the local ethics committee approved an amendment to the original application for review of medical records and data collection without the patients' informed consent.

Disclosure Statement

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Author Contributions

Study conception and design: K. Fröss-Baron and A. Sundin. Provision of patients: K. Fröss-Baron, S. Welin, D. Granberg, B. Eriksson, and T. Khan. Collection and/or assembly of data: K. Fröss-Baron, U. Garske-Roman, M. Sandström, and A. Sundin. Data analysis and interpretation: K. Fröss-Baron and A. Sundin. Drafting of the manuscript: K. Fröss-Baron and A. Sundin. Critical revision of the manuscript: U. Garske-Roman, S. Welin, D. Granberg, B. Eriksson, T. Khan, M. Sandström, and A. Sundin. All authors agreed with the final version of the manuscript.

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