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Effectiveness, safety, and retreatment outcomes in GEP-NET patients undergoing ^{177}Lu-based PRRT: a ten-year real-world experience

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Abstract

Background Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-labeled somatostatin analogues is an established and increasingly applied treatment for advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs). We report results focusing on effectiveness, short-term safety, and retreatment outcomes, based on ten years of clinical experience from an Austrian center of expertise, including patients referred for retreatment after prior therapy elsewhere.

Methods This retrospective study included 49 patients treated with ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC between 2014 and 2023. Subgroups included patients receiving their first PRRT course at our center (n = 45). Of this initial-treatment cohort, 9 patients subsequently underwent PRRT retreatment at our center. Additionally, 4 external patients previously treated with ^{90}Y-PRRT at another institution were referred for ^{177}Lu-based retreatment, resulting in a total retreatment subgroup of 13 patients. Overall survival (OS), progression-free survival (PFS), and selected laboratory toxicity parameters were evaluated according to CTCAE v5.0.

Results In the GEP-NET group, the median number of PRRT cycles was 4 with a median cumulative activity of 27.9 GBq. Median OS was 54.2 months (95% CI: 33.2–upper bound not reached), and median PFS was 24.1 months (95% CI: 11.8–36.1). PET-CT-based response assessment was available in 36 of 45 patients. Using evaluable patients as denominator, the exploratory visual SSTR-PET-CT-based objective response rate was 30.6%. Considering the entire initial-treatment cohort and assuming patients without follow-up imaging were non-responders, the ORR was 24.4%. Grade 3 or higher hematologic toxicity occurred in 4.4% of patients with one case each of grade 3 anemia and grade 4 leukopenia while no grade 3 or higher renal toxicity was observed. One patient (2%) developed myelodysplastic syndrome (MDS), followed by acute myeloid leukemia (AML). In the retreatment group (median 4 additional cycles), the median PFS was 18.1 months (95% CI: 8.6–24.6) and the ORR was 30.8% (n = 13). No grade ≥3 toxicities or hematologic malignancies were observed.

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Conclusion PRRT at our institution showed clinical outcomes and a favorable short-term safety profile broadly consistent with previously published PRRT studies. These findings support the role of PRRT in routine clinical practice. Retreatment outcomes appeared encouraging in selected patients but should be interpreted as exploratory given the limited cohort size, retrospective design, and absence of formal comparative analysis.

Keywords GEP-NET, PRRT, Theranostics, Lutetium-177, Safety

Introduction

Neuroendocrine tumors (NETs) are heterogeneous malignancies that predominantly arise as gastroenteropancreatic NETs (GEP-NETs). Although considered rare, a prospective Austrian registry study reported annual incidence rates of approximately 2.5 per 100,000 for men and 2.4 per 100,000 for women, with the majority of these neuroendocrine neoplasms (NENs) being well-differentiated NETs [1]. Up to 80% of GEP-NETs express somatostatin receptors, which serve as targets for both diagnostic imaging and targeted therapy through peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-labeled peptides [2]. Since its introduction, PRRT has consistently demonstrated high effectiveness and a favorable safety profile across multiple studies for patients with somatostatin receptor-positive NETs in an advanced or metastatic setting [3–6]. In the pivotal phase III NETTER-1 trial, ^{177}Lu-DOTATATE significantly prolonged progression-free survival (PFS) compared with high-dose octreotide and showed a trend toward longer overall survival (OS) [7]. While major prospective trials have established PRRT as a standard of care, real-world data are critical to complement these findings, typically reporting median PFS ranging from 20 to 40 months and disease control rates above 70%, with serious hemato- or renal toxicity typically below 10% [8–11].

Although the efficacy and safety of ^{177}Lu-based PRRT have been established in prospective trials and supported by several European real-world studies, important questions regarding outcomes and retreatment strategies remain incompletely characterized. In particular, data on PRRT retreatment are less extensive than those available for initial treatment, despite its increasing use in clinical practice following disease progression. Furthermore, patients treated in routine care frequently represent more heterogeneous populations than those enrolled in prospective clinical trials, often receiving individualized treatment schedules and management approaches. Additional long-term real-world data may therefore provide complementary information regarding treatment effectiveness, safety, and retreatment outcomes in everyday practice. The present study reports a ten-year single-center experience with ^{177}Lu-based PRRT in patients with gastroenteropancreatic neuroendocrine tumors, including both initial treatment and retreatment cohorts. By evaluating clinical outcomes and treatment-related toxicity in a real-world setting, this study aims to contribute further evidence on the use of PRRT and the feasibility of retreatment strategies.

Materials and methods

Study design

A retrospective, single-center cohort study was conducted at the Department of Nuclear Medicine, Ordensklinikum Linz, Austria. All patients who received their first PRRT cycle between June 2014 (initiation of PRRT at our center) and September 2023 were enrolled. Somatostatin receptor-positive (SSTR-positive) PET-CT was required for treatment eligibility.

Patient characteristics and inclusion criteria

All 49 patients aged 18 years or older with histologically confirmed GEP-NETs who received at least one cycle of ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC PRRT in the observational period were eligible for inclusion. Additional inclusion criteria required that patients had a complete clinical history ($n = 49$) and that all relevant routine clinical data were available for analysis ($n = 49$). For further analysis, two subgroups were defined: One comprising patients receiving PRRT for the first time ($n = 45$), and another including 13 patients receiving PRRT retreatment after progression following the initial PRRT course. Of these, 4 patients had received their initial PRRT course with ^{90}Y-labelled peptides at another institution before being admitted for treatment reinduction to our center. Consequently, the retreatment subgroup ($n = 13$) partially overlaps with the main cohort ($n = 9$ initial patients retreated at our center) and incorporates external treatment heterogeneity ($n = 4$ patients with prior ^{90}Y-PRRT elsewhere). This structural composition must be taken into account when interpreting the retreatment outcomes. While acknowledging the different physical properties and toxicity profiles of ^{90}Y and ^{177}Lu, these patients were included to reflect the clinical reality of a specialized center. Patient inclusion and the definition of the retreatment group are summarized in a study flow diagram (Fig. 1).

Treatment protocol

Treatment was administered according to the German S1 guidelines [12]. While the international standard regimen typically consists of 4 cycles, the standard intended protocol at our institution allowed for up to 6 cycles (target activity 7.4 GBq per cycle, spaced 8–12 weeks apart).

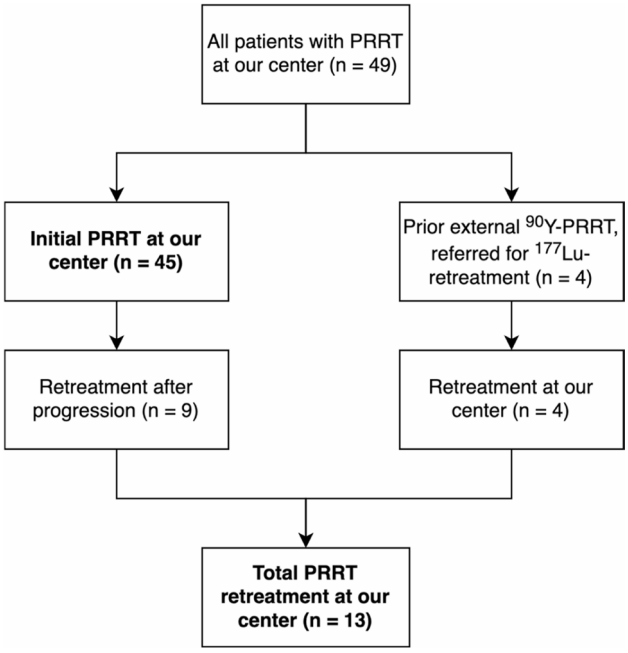


Fig. 1 Patient flow diagram

This approach was based on local clinical practice and aimed to maximize cumulative therapeutic activity while maintaining acceptable toxicity. Continuation beyond four cycles was contingent on treatment tolerance, preserved renal and hematologic function, absence of clinically relevant toxicity, and ongoing expected clinical benefit as determined by the treating physicians and multidisciplinary tumor board. Permanent discontinuation was triggered by disease progression, Grade ≥ 3 toxicity, or patient refusal. For transient Grade 3 hematotoxicity or a clinically relevant eGFR decline, cycles resumed with a 25–50% dose reduction. Crucially, all treatment modifications, dose reductions, or decisions to extend therapy up to 6 cycles were based on the patient's individual clinical status, performance status, laboratory values, and a specialized nuclear medicine departmental consensus. ^{177}Lu-DOTATATE was applied as the primary agent until June 26, 2018. From May 24, 2018, ^{177}Lu-DOTATOC became the standard compound. Treatment regimens were adjusted based on individual patient characteristics such as performance status (ECOG), renal function, and comorbidities. In patients with an impaired organ function or limited performance status, the activity per cycle was reduced to minimize the risk of severe toxicity-related adverse events. Prior to each treatment cycle, patients underwent a standardized laboratory testing, including white blood cell count, hemoglobin, platelets, creatinine, estimated glomerular filtration rate (eGFR), chromogranin A, and neuron-specific enolase (NSE). Renal function was further assessed via ^{99}mTc-MAG3 scintigraphy to ensure treatment safety. To minimize nephrotoxicity, patients received an intravenous infusion of 25 g L-arginine and 25 g L-lysine in 1000 mL saline during PRRT administration. Standard antiemetic and supportive medications were administered prior to each cycle. Following each cycle, SPECT-CT imaging was performed to evaluate tumor uptake and biodistribution. Dosimetry was performed after the first cycle to monitor organs at risk, focusing strictly on the kidneys. These dosimetric findings were used as a descriptive safety framework in clinical routine. Tumor dosimetry and standardized cumulative absorbed dose estimates were not systematically available. Therefore, dosimetry data were not used for response prediction or outcome-based analyses. For treatments administered prior to July 2023, dosimetric calculations were conducted using OLINDA/EXM, while HERMES Medical Solutions was utilized for subsequent cases. Laboratory tests were performed one day before each PRRT cycle and repeated between 2 and 8 weeks after therapy. Follow-up imaging (PET-CT) was performed every 3–6 months, depending on tumor grade and clinical status. Response was assessed in an exploratory manner on serial hybrid SSTR-PET-CT scans, integrating both visual comparison of tumor tracer uptake (relative to physiological liver and spleen uptake) and the evaluation of structural changes on the diagnostic CT component of the scans. Furthermore, ^{18}F-FDG PET-CT was utilized case-by-case in G3 tumors to detect dedifferentiation.

PRRT retreatment was considered in selected patients after documented disease progression following prior PRRT. No rigid minimum interval was mandated. However, the interval from prior PRRT, prior treatment tolerance, disease dynamics, organ function, and available systemic alternatives were considered in the individual decision-making process. The clinical indication for retreatment required documented disease progression on serial hybrid SSTR-PET-CT imaging after a period of prior stable disease. Decisions regarding patient eligibility were made on an individual case-by-case basis within an interdisciplinary tumor board, requiring generally preserved renal and hematological function without predefined rigid laboratory cut-offs.

Methods

PFS was defined as the time from the first day of PRRT until documented disease progression or death from any cause, whichever occurred first. Progression was considered present in cases of newly detected tumor lesions, clear structural tumor growth on the CT component, or visually evident increase in tumor tracer uptake on serial SSTR-PET-CT imaging. No validated PET-based response criteria or retrospective RECIST 1.1-based assessment were available. OS was defined as the time from the first PRRT administration until death or the

date of last follow-up for censored patients. The median follow-up time for the study cohorts was estimated using the reverse Kaplan-meier method. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The reported values represent the highest grade observed between the first PRRT cycle and the last standardized laboratory follow-up (2–8 weeks after the final cycle). Secondary malignancies, such as MDS and AML, were assessed throughout the full observational period from treatment initiation until death or last follow-up.

Table 1 Baseline patient, tumor and treatment characteristics of GEP-NET patients undergoing initial and retreatment PRRT

	GEP-Initial group	GEP-Retreatment subgroup
N	45	13
Demographics		
Age (years, median, IQR)	63.7 11.3	65.2 13.9
Male sex, n (%)	25 (55.6)	9 (69.2)
Primary tumor site, n (%)		
Pancreas	20 (44.4)	6 (46.2)
Ileum	10 (22.2)	4 (30.8)
Small intestine	8 (17.8)	1 (7.7)
Not classified	5 (11.1)	2 (15.4)
Right colon, Appendix	2 (4.4)	0
WHO grade, n (%)		
G1	14 (31.1)	5 (38.5)
G2	27 (60.0)	7 (53.8)
G3	3 (6.7)	1 (7.7)
Not specified	1 (2.2)	0
Clinical status		
ECOG 0–1	34 (75.6)	11 (84.6)
ECOG ≥ 2	2 (4.4)	0
ACCI (median, range)	9 (7–15)	8 (7–13)
Treatment characteristics		
Median time from diagnosis to PRRT, years	2.26	5.15
Median number of prior systemic lines	1 (0–2)	2 (1–4)
Somatostatin analogs	36 (80.0)	10 (76.9)
Targeted therapy	5 (11.1)	6 (46.2)
Chemotherapy	4 (8.9)	1 (7.7)
Only ^{177}Lu-DOTATOC	33 (73.3)	12 (92.3)
Only ^{177}Lu-DOTATATE	10 (22.2)	1 (7.7)
Both compounds	2 (4.4)	0
Median PRRT cycles	4	4
Mean PRRT cycles	4.04	3.85
Cycle distribution		
< 4 cycles	11	3
4 cycles	16	7
5 cycles	13	2
6 cycles	5	1
Median cumulative total activity (GBq)	27.9	27.4
Mean absorbed kidney dose right (Gy)	2.60 ± 1.37	2.42 ± 1.37
Mean absorbed kidney dose left (Gy)	2.50 ± 1.33	2.71 ± 1.97

Values are expressed as n (%) unless otherwise specified

ACCI Age-adjusted Charlson Comorbidity Index, *ECOG* Eastern Cooperative Oncology Group performance status, *PRRT* peptide receptor radionuclide therapy, *GEP* gastroenteropancreatic, *WHO* World Health Organization

Data management and statistics

Clinical, laboratory, and imaging data were extracted from institutional records and pseudonymized for analysis. Survival data were obtained from the hospital's cancer registry. Statistical analyses were performed using Stata/BE 18.0. Kaplan–Meier curves were generated for OS and PFS. Patient characteristics were evaluated descriptively. Baseline comorbidities and age were quantified using the age-adjusted Charlson Comorbidity Index (ACCI) [13]. The objective response rate (ORR) was assessed exploratorily and was defined as the proportion of evaluable patients with complete remission or partial response on serial SSTR-PET-CT. Complete remission was defined as disappearance of pathological tumor tracer uptake in all previously detected lesions. Partial response was defined by visually evident reduction of tumor tracer uptake and/or tumor burden on serial SSTR-PET-CT, without the appearance of new lesions. These assessments were exploratory and were not based on validated PET response criteria or retrospective RECIST 1.1 assessment. Response assessment was performed at a standardized timing of every three to six months. A statistical comparison of OS/PFS between initial and retreatment cohorts was not feasible due to overlapping populations and selection bias.

Results

Patient characteristics

In total, 152 treatment cycles were administered in the GEP-NET initial group. In the collective of 13 retreated patients, 44 cycles were delivered. The median age at treatment initiation was 63.7 years (IQR: 11.3) in the GEP Initial group and 65.2 years (IQR: 13.9) in the retreatment group (Table 1). Male patients were slightly overrepresented (55.6% and 69.2%, respectively). Median time from initial diagnosis to PRRT was 2.26 years in the initial treatment group and 5.15 years in the retreatment group. The median interval between the last cycle of initial PRRT and the first retreatment cycle was 28.4 months (range 4.6–44.7 months), with two patients receiving retreatment within < 8 months due to rapid progression. Four patients received their initial therapy externally, and the exact interval could therefore not be determined. Targeted therapy with Everolimus or Sunitinib was documented for 11.1% and 46.2% of patients in the respective groups. PRRT was performed using either ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC, with the majority of cycles (82.3%) involving ^{177}Lu-DOTATOC. The median number of cycles administered was 4 (range 1–6) for the initial

treatment group and 4 (range 1–4) for the retreatment group. The majority of patients received somatostatin analogues during treatment, with lanreotide being used approximately twice as frequently as octreotide.

Safety and adverse events/toxicity

In the GEP-NET group, grade 3 (per CTCAE v5.0) or higher hematologic toxicity occurred in 4.4% of patients. Specifically one case of grade 3 anemia and one case of grade 4 leukopenia were observed. No grade ≥ 3 thrombocytopenia or nephrotoxicity was reported (Table 2). One patient (2%) developed myelodysplastic syndrome (MDS) 40 months after the first PRRT cycle followed by acute myeloid leukemia (AML), leading to death after 67 months. This patient had received five cycles of ^{177}Lu-DOTATATE with a cumulative activity of 32.9 GBq and presented with baseline thrombocytosis (525 G/L). The patient had a oncological pre-history, having been treated for an adenocarcinoma of unknown primary with capecitabine and temozolomide as well as bevacizumab prior to PRRT.

In the retreatment group, no grade 3 or 4 hematologic or renal toxicities occurred, and no cases of MDS or AML were observed during follow-up.

Treatment effectiveness

GEP-NET initial treatment group (n = 45)

The median number of PRRT cycles administered per patient was 4. The median progression-free survival (PFS), calculated from the first PRRT cycle to progression on PET-CT, was 24.1 months (95% CI: 11.8–36.1; SE: 5.0), with 31 events observed (Fig. 2). The median overall survival (OS) from the first PRRT cycle was 54.2 months (95% CI: 33.2–not reached; SE: 14.1), based on 19 deaths (Fig. 3). Response assessment was available in 36 of 45 patients. Using evaluable patients as denominator, the exploratory visual SSTR-PET-CT based ORR was 30.6% (11/36). Considering the entire initial-treatment cohort and assuming patients without follow-up imaging were non-responders, the ORR was 24.4% (11/45). Median follow-up was 43.0 months, estimated using the reverse Kaplan-Meier method.

Table 2 Hematologic and renal toxicity according to CTCAE v5.0 in patients undergoing initial and retreatment PRRT

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GEP-Initial group (*n* = 45)					
Leukopenia	24 (53.5)	19 (42.2)	1 (2.2)	0	1 (2.2)
Anemia	10 (22.2)	28 (62.2)	6 (13.3)	1 (2.2)	0
Thrombocytopenia	28 (62.2)	16 (35.6)	1 (2.2)	0	0
Elevated serum creatinine	22 (48.9)	17 (37.8)	6 (13.3)	0	0
GEP-Retreatment subgroup (*n* = 13)					
Leukopenia	7 (53.8)	5 (38.5)	1 (7.7)	0	0
Anemia	3 (23.1)	7 (53.8)	3 (23.1)	0	0
Thrombocytopenia	13 (100)	0	0	0	0
Elevated serum creatinine	6 (46.2)	5 (38.5)	2 (15.4)	0	0

Values are given as n (%). Toxicities were graded according to Common Terminology Criteria for Adverse Events (version 5.0)

GEP-NET retreatment group (n = 13)

A total of 13 patients received PRRT retreatment after documented disease progression following the first PRRT course, with a median of 4 additional cycles administered. The median PFS after retreatment, measured from the first retreatment cycle to PET-CT-confirmed progression, was 18.1 months (95% CI: 8.6–24.6; SE: 5.4), with 10 progression events recorded (Fig. 4). At the time of analysis, 4 deaths had occurred in this subgroup, and the median OS after retreatment could not yet be determined (Fig. 5). ORR was 30.8% among all patients determined via an exploratory SSTR-PET-CT-based assessment (4/13).

Discussion

According to current international guidelines, such as those from the European Neuroendocrine Tumor Society (ENETS) and the European Society for Medical Oncology (ESMO), ^{177}Lu-based PRRT is an established treatment option for patients with progressive, metastatic, well-differentiated GEP-NETs [14, 15]. In line with these recommendations, our single-center analysis observed clinical outcomes and a short-term safety profile broadly consistent with existing literature. These findings add real-world evidence from an Austrian tertiary referral center, including data on PRRT retreatment, an area in which available evidence remains comparatively limited.

In our single-center cohort for GEP-NET initial group (n = 45), the median overall survival (OS) from the start of ^{177}Lu-PRRT was 54.2 months (95% CI: 33.2 months – not reached). This outcome was broadly within the range reported in major PRRT studies, including NETTER-1. However, direct comparisons must be interpreted with caution because of differences in study design, patient populations, treatment regimen, imaging methodology, and response assessment [16]. For instance, NETTER-1 was restricted to midgut G1–G2 tumors and a fixed four-cycle regimen, whereas our real-world cohort included pancreatic NETs and up to six treatment cycles.

We observed a median progression-free survival (PFS) of 24.1 months (95% CI: 11.8–36.1) assessed via PET-CT, with a 20-month PFS rate of 76.6%. This 20-month PFS rate was numerically higher than the 65.2% reported in NETTER-1. Nevertheless, direct comparison is limited by the methodological differences outlined above. Comparatively, in a large single-center series of 443 midgut NET patients treated with ^{177}Lu-PRRT, Brabander et

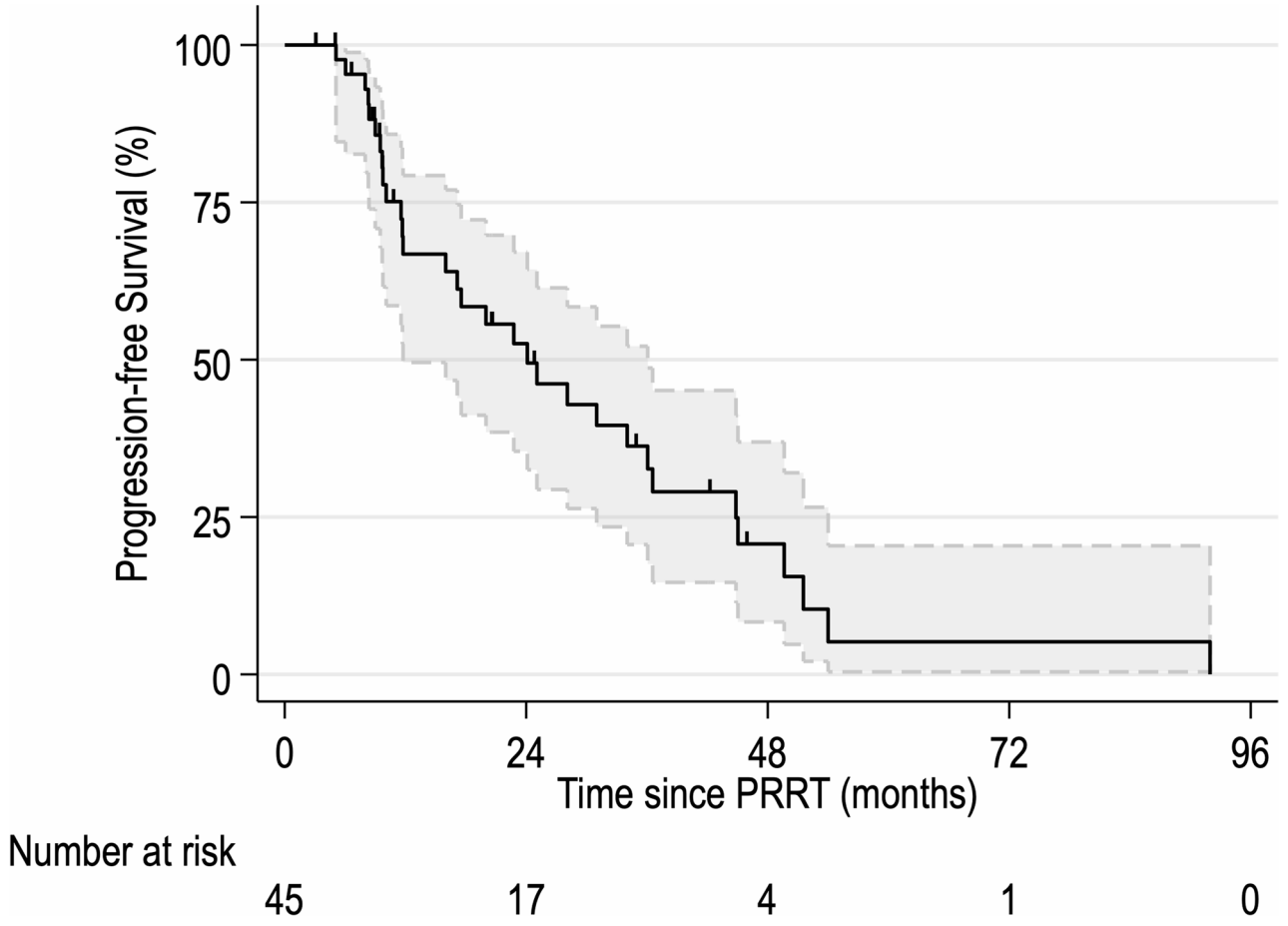


Fig. 2 Kaplan–Meier curve showing progression-free survival (PFS) from the first cycle of PRRT in the GEP-Initial group ($n = 45$). The median PFS was 24.1 months (95% CI: 11.8–36.1; SE: 5.0)

al. reported a median OS of 63 months (95% CI, 55–72 months) and PFS of 29 months (95% CI, 26–33 months) [8]. In contrast, our mixed GEP-NET cohort included both midgut and pancreatic primaries and a small subset of grade 3 tumors, which may account for the shorter PFS observed.

Similarly, prospective NETTER-2 trial — which included 66% grade-2 and 34% grade-3 NETs, with 54% pancreatic primaries — reported a median PFS of 22.8 months (95% CI: 19.4–not reached). While not directly comparable due to differences in tumor grading and primary site distribution, our cohort showed a similar median PFS of 24.1 months (95% CI: 11.8–36.1), with 31.1% grade 1, 60% grade 2, and 6.7% grade 3 tumors, and 44.4% pancreatic NETs [17].

Long-term effectiveness data were also reported by Gabriel et al., who followed 44 NET patients (mean 5–6 cycles, cumulative ~ 27 GBq) over a median of 80 months and observed a median OS of 79 months, underscoring the durability of PRRT effects [18]. In our cohort, median OS was 54.2 months, which is lower, likely due to differences in tumor grade and primary tumor site distribution.

Regarding patient selection, our institution employed ^{68}Ga-DOTANOC PET-CT not only for staging but also for treatment eligibility and response monitoring. This approach reflects findings by Gabriel et al. demonstrating the superiority of PET-CT over conventional scintigraphy in lesion detection, staging accuracy, and predicting response to PRRT [19]. While SSTR-PET-CT provides functional information beyond purely morphological imaging and reflects routine clinical practice at our institution, PET-based response assessment remains insufficiently standardized for outcome reporting in PRRT studies. Because response and progression were assessed using an exploratory visual SSTR-PET-CT-based approach rather than validated PET response criteria or RECIST 1.1, both ORR and PFS should be interpreted descriptively and are not directly comparable with RECIST-based outcomes from prospective trials [20]. The PET-CT-based ORR was 30.6% among evaluable patients and 24.4% when the entire initial-treatment cohort was used as denominator. These findings are

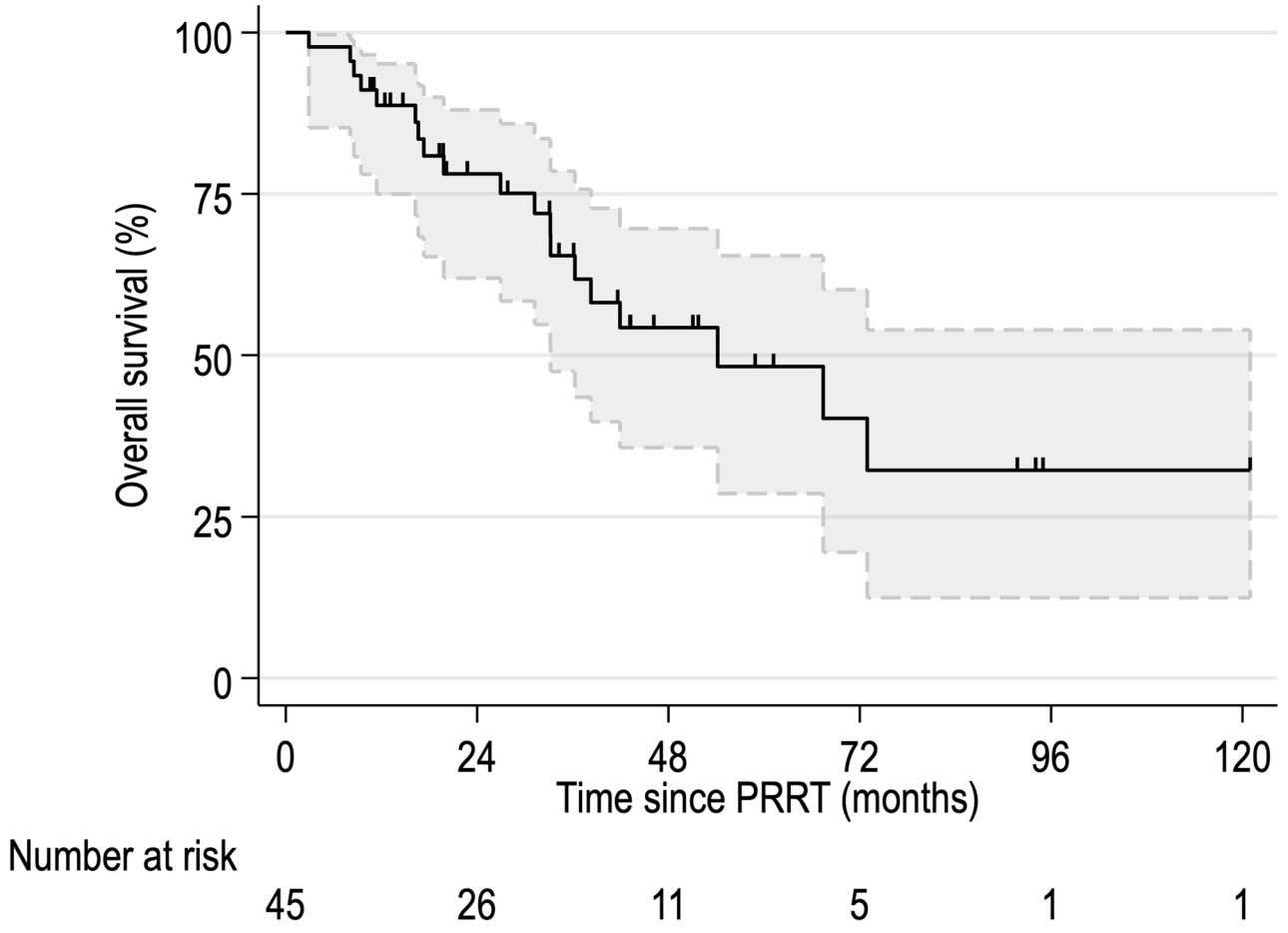


Fig. 3 Kaplan–Meier curve showing overall survival (OS) from the first cycle of PRRT in the GEP-Initial group ($n = 45$). The median OS was 54.2 months (95% CI: 33.2 months – not reached; SE: 14.1). Censored patients are indicated by tick marks on the curve

broadly compatible with published PRRT experiences. However, direct comparison with NETTER-1 (18%), NETTER-2 (43%), and the Erasmus Medical Center cohort (39%) remains limited by the methodological differences outlined above, particularly the PET-CT-based response assessment used in our cohort [8, 16, 17].

Regarding short-term safety and adverse events in the GEP-Initial group, grade 3 or higher toxicities occurred in 4.4% of patients, which was limited to single cases of leukopenia and anemia. Notably, no grade 3 events were observed for thrombocytopenia or elevated serum creatinine. In comparison, NETTER-1 reported grade ≥ 3 leukopenia and thrombocytopenia in 1% and thrombocytopenia in 2% of patients [7]. In NETTER-2, lymphopenia was the most common hematotoxicity (5%), while leukopenia, anemia and thrombocytopenia were rare [17].

A retrospective cohort from the Erasmus Medical Center (n = 582) reported slightly higher rates: grade ≥ 3 thrombocytopenia in 5.2%, leukopenia in 5.5%, anemia in 4% [8].

One patient (2%) developed MDS 40 months after the first PRRT cycle. Given the prior exposure to alkylating chemotherapy this case is likely multifactorial. This is consistent with Al-Toubah et al. who reported an increased therapy-related myeloid neoplasms risk of ~ 8% for sequential CapTem and PRRT [21]. Death occurred 67 months after treatment initiation due to MDS progressing to AML. The reported incidence of MDS/AML in NETTER-1, NETTER-2, and Brabander et al. ranges from 1% to 1.5% [8, 16, 17]. The low incidence of severe acute toxicity observed in our cohort is consistent with published PRRT series and may partly reflect careful patient selection, including preserved renal function prior to treatment. However, standardized laboratory toxicity assessment was limited to 2–8 weeks after the final treatment cycle and therefore primarily captured short-term toxicity. Consequently, delayed hematologic or renal adverse events may be underrepresented despite routine long-term oncological follow-up.

Disease progression following initial PRRT is a common clinical scenario in advanced GEP-NETs. Consequently, retreatment with PRRT has emerged as a valuable option for patients with limited systemic treatment alternatives [22, 23]. However, most available

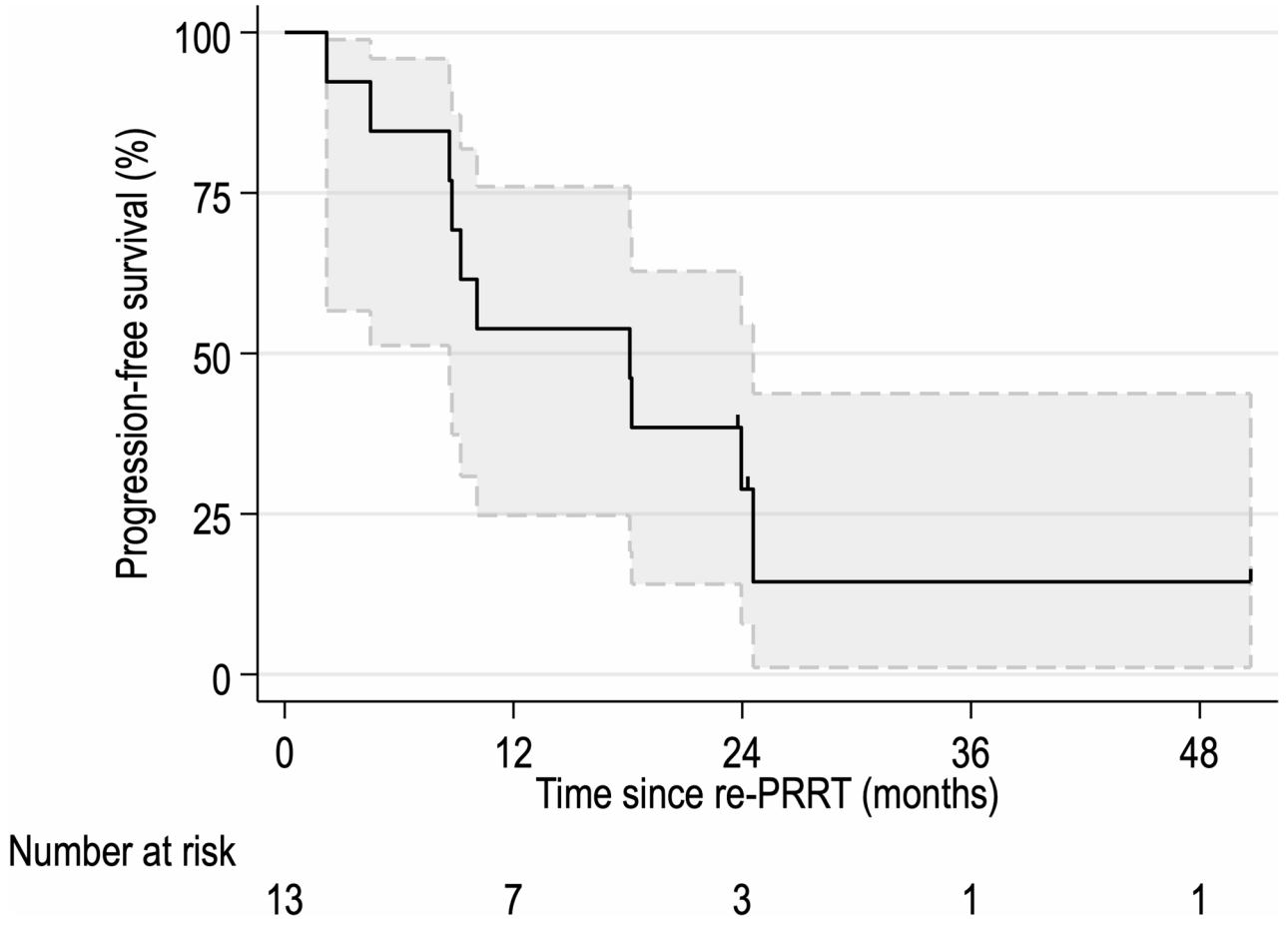


Fig. 4 Kaplan–Meier curve showing progression-free survival (PFS) from the first cycle of PRRT retreatment in the GEP-Retreatment subgroup ($n = 13$). The median PFS was 18.1 months (95% CI: 8.6–24.6; SE: 5.4), with a median follow-up of 45.0 months after retreatment

evidence is derived from retrospective, single-center studies, and results should be interpreted with caution. Accordingly, our retreatment analysis should be regarded as exploratory given the limited sample size, absence of formal comparative analysis, and cohort heterogeneity. Furthermore, four patients in the retreatment cohort had previously received ^{90}Y-based PRRT at external institutions. In our cohort, 13 patients received a median of 4 additional cycles and up to 11 cycles of PRRT. The median PFS after retreatment was 18.1 months (95% CI: 8.6–24.6). No patients developed MDS or AML during the observation period. While 4.4% of the initial group experienced grade ≥ 3 hematologic toxicity and no grade ≥ 3 renal toxicity, no grade ≥ 3 hematologic or renal adverse events occurred during retreatment. This finding should be interpreted cautiously and may reflect selection bias, as retreatment was considered only in patients with adequate organ function, acceptable performance status, persistent SSTR expression, and absence of prohibitive toxicity from previous PRRT. These results stand in line with previously published retrospective studies. An Indian study (n = 26) reported a median PFS of 17 months and no grade ≥ 3 adverse events during a median follow-up of 72 months [24]. Similarly, another study that mainly administered ^{90}Y-DOTATATE (n = 49) reported a median PFS of 17.5 months (95% CI: 11.0–23.8), with grade ≥ 3 bone marrow or renal toxicity occurring in 2.4% of patients [25]. In contrast, Rudisile et al. reported a markedly shorter median PFS of 6 months (95% CI: 0–16; 8/32 patients censored), with retreatment being initiated after a median interval of 39 months (range: 13–85 months) [26]. Differences in patient selection, retreatment timing, imaging methodology, and cohort characteristics may have contributed to the variability in reported PFS outcomes across studies. Therefore, the retreatment findings should be interpreted as descriptive real-world observations rather than definitive evidence of retreatment efficacy.

A meta-analysis by Strosberg et al. that included 414 patients showed a pooled median PFS of 12.52 months (95% CI: 9.82–15.22), with grade ≥ 3 toxicity occurring in 5% (95% CI: 2–8) of patients [22]. The higher PFS (18.1 months) observed in our cohort should be interpreted in the context of careful patient selection, sustained

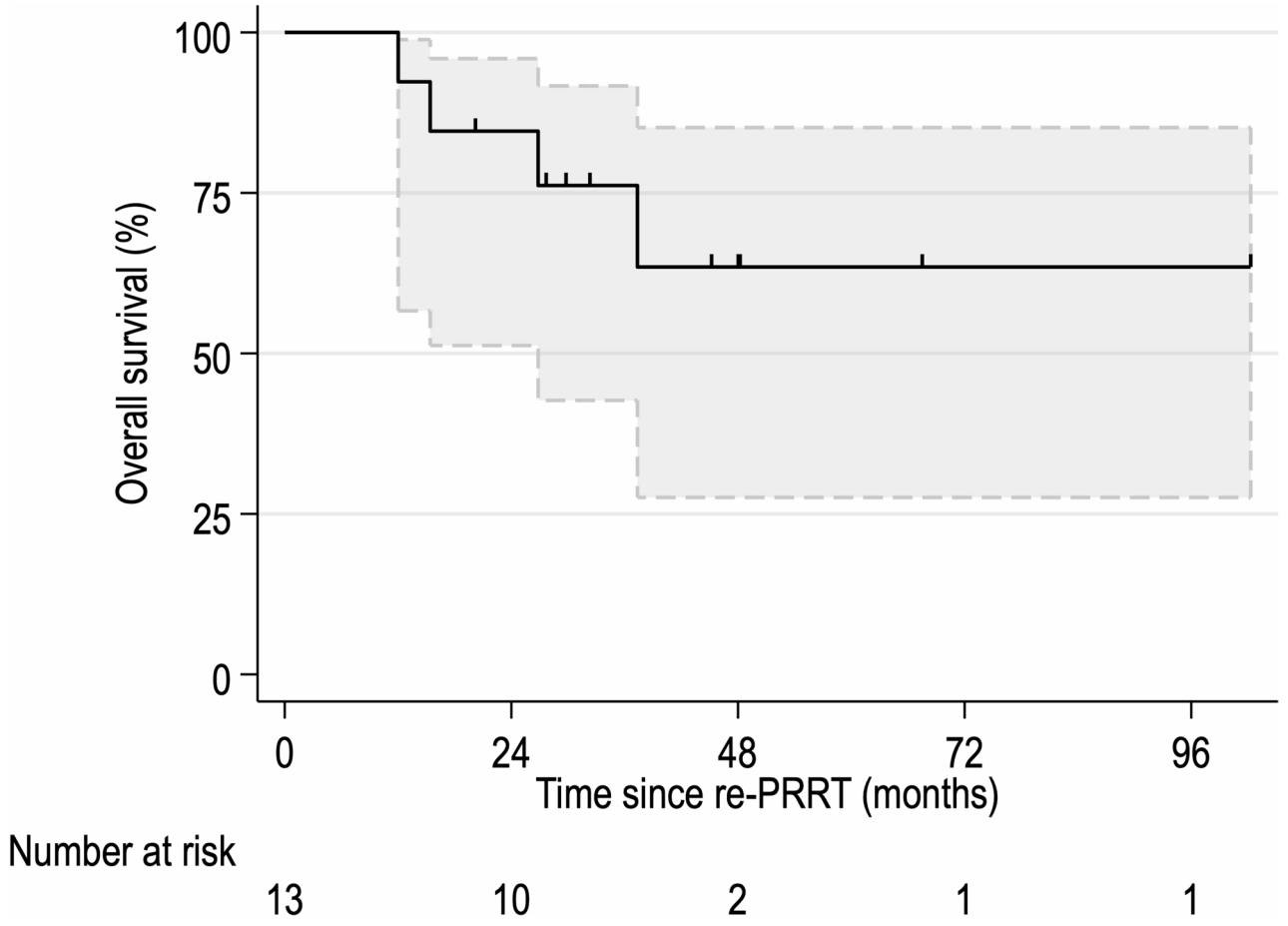


Fig. 5 Kaplan–Meier curve showing overall survival (OS) from the first cycle of PRRT retreatment in the GEP-NET group ($n = 13$). After a median follow-up of 45.0 months after retreatment, 4 events were observed, and the median OS could not be estimated

somatostatin receptor expression, and the exploratory nature of the retreatment analysis. Given the increasing clinical relevance of PRRT retreatment, prospective studies are underway to confirm its effectiveness and safety in a controlled setting [27].

Strengths and limitations

This retrospective, single-center study provides real-world experience on both initial and retreatment PRRT in GEP-NETs. Strengths include comprehensive documentation, PET-CT-based assessment, and consistent toxicity grading. Limitations include the retrospective design, small retreatment cohort, heterogeneous primary tumor sites, variable follow-up intervals, and the absence of a control group. The use of both ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC was not analyzed separately and may have introduced additional variability. Furthermore, the inclusion of four patients in the exploratory retreatment cohort who had previously received ^{90}Y-based PRRT at another institution introduced biological and dosimetric heterogeneity. Given the small size of the retreatment subgroup ($n = 13$), the potential influence of prior ^{90}Y-based therapy on retreatment outcomes could not be assessed separately. Response assessment was based on exploratory SSTR-PET-CT findings rather than standardized RECIST 1.1 criteria, limiting direct comparison with major prospective PRRT trials. In addition, dosimetry was limited to first-cycle kidney dosimetry and served as a descriptive safety framework. Tumor dosimetry and standardized cumulative absorbed dose estimates were not systematically available. Dosimetry was performed using different software platforms over the study period, potentially introducing methodological variability. Therefore, dosimetry findings should be interpreted descriptively, and no conclusions regarding dose-response relationships or absorbed dose-outcome associations can be drawn. The standardized laboratory follow-up window of 2–8 weeks after the final treatment cycle primarily captured short-term laboratory toxicities. Consequently, delayed hematologic and renal toxicity may have been incompletely captured despite routine long-term oncological follow-up. Although long-term toxicities, including one case of MDS diagnosed 40 months after initial PRRT, were identified through

routine clinical follow-up, subtle chronic declines in renal function may have been incompletely captured due to the lack of continuous study-specific monitoring. Finally, the inclusion of patients treated over a 10-year period may have introduced treatment-era heterogeneity related to evolving clinical practice, patient selection, and supportive care measures, potentially affecting the generalizability of the findings.

Conclusion

This single-center retrospective study supports the clinical effectiveness and favorable short-term safety profile of ^{177}Lu-based PRRT in patients with advanced GEP-NETs treated in routine clinical practice. Clinical outcomes and short-term toxicity rates were broadly consistent with previously published real-world series, and observed survival outcomes were within the range reported in major PRRT studies. In the initial treatment setting, PRRT was associated with meaningful disease control and a low incidence of severe short-term toxicity. Furthermore, in this small exploratory retreatment cohort, PRRT retreatment was associated with encouraging clinical outcomes and an acceptable short-term safety profile. However, given the retrospective design, limited sample size, cohort heterogeneity, exploratory PET-based response assessment, and restricted long-term toxicity follow-up, these findings should be interpreted with caution. Larger prospective studies are warranted to further evaluate long-term outcomes and to better define the role of PRRT retreatment in clinical practice.

Abbreviations

AML	Acute Myeloid Leukemia
ACCI	Age-adjusted Charlson Comorbidity Index
CapTem	Capecitabine/Temozolomide
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CT	Computed Tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
ECOG	Eastern Cooperative Oncology Group
ENETS	European Neuroendocrine Tumor Society
ESMO	European Society for Medical Oncology
GCP	Good Clinical Practice
GEP-NETs	Gastroenteropancreatic Neuroendocrine Tumors
IQR	Interquartile Range
MDS	Myelodysplastic Syndrome
NETs	Neuroendocrine Tumors
ORR	Overall Response Rate
PET	Positron Emission Tomography
RECIST	Response Evaluation Criteria in Solid Tumors
SE	Standard Error
SPECT	Single Photon Emission Computed Tomography
SSTR	Somatostatin Receptor
WHO	World Health Organization

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Authors' contributions

Study concept and design (L. T., H. R. and J. D), acquisition of data (L. T., J. D and H. R.), analysis and interpretation of data (all authors), drafting of the manuscript (L. T., P. T. and H. R.), critical revision of the manuscript for intellectual content (all authors).

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Data availability

The datasets generated during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines. Ethical approval was obtained from the Ethics Committee of the Johannes Kepler University Linz, local ethic number 1285/2023, signed 20-11-2023. The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study and the use of pseudonymised data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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