

Real-World Outcomes of [¹⁷⁷Lu]Lu-DOTA-TATE Peptide Receptor Radionuclide Therapy in Patients with Metastatic Gastroenteropancreatic Neuroendocrine Tumors: Data from a Belgian ENETS Center of Excellence

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Abstract

Background and study aims: Peptide receptor radionuclide therapy (PRRT) has been reimbursed in Belgium since 2022. Post marketing monitoring of efficacy in Belgian context has not yet been performed. This study aimed to evaluate the efficacy and safety of PRRT in patients with progressive metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Patients and methods: Our retrospective analysis included GEP-NET patients who received at least one cycle of [¹⁷⁷Lu]Lu-DOTA-TATE at Institute Jules Bordet (Brussels, Belgium) between 2013 and 2023. Treatment response was assessed according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier analysis. Treatment safety profiles were reported descriptively.

Results: Following initial PRRT (PRRT-1), in 110 patients with progressive metastatic GEP-NETs (grades 1-3), median PFS was 22.5 months (95% CI: 19.7–29), and median OS was 42.3 months (95% CI: 34.3–55). RECIST 1.1 responses were complete response in 1%, partial response in 21.6%, stable disease in 60.8%, and progression in 16.7% of patients. Median time of follow-up post PRRT-1 was 26.4 months (range: 0.8 – 106.4). Grade 3-4 anemia, leukopenia, lymphopenia and thrombocytopenia occurred in 1.9%, 2.8%, 50.5% and 2.8% of patients, respectively. Two patients (1.8%) developed myelodysplastic syndrome. Grade 3 or 4 renal toxicity was observed in two patients who had impaired renal function prior to PRRT.

Conclusion: Post-marketing analysis in an ENETS Center of Excellence confirmed that the efficacy and safety of PRRT in GEP-NETs are consistent with phase 3 trial data. (*Acta gastroenterol belg.*, 2026, 89, 13-24).

Keywords: [¹⁷⁷Lu]Lu-DOTA-TATE; gastroenteropancreatic neuroendocrine tumors; peptide receptor radionuclide therapy.

Introduction

According to a recent cross-sectional analysis using data from Surveillance, Epidemiology, and End Results (SEER) program from 1975 to 2021, the age-adjusted incidence of neuroendocrine neoplasms (NENs) increased 5.2-fold, reaching 8.52 cases per 100,000 in 2021, in association with an increased diagnosis of early-stage disease. Gastroenteropancreatic NENs (GEP-NENs) accounted for 6.1 cases per 100,000, with small bowel NENs being the most common subtype within this group (1.4 per 100,000) (1). Based on histopathological criteria, GEP-NENs are classified into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) (2,3). Furthermore, NETs are graded according

to mitotic count and Ki67 index as follows: low-grade G1 NETs (<2 mitoses/2 mm² and/or Ki67 < 3%), intermediate-grade G2 NETs (2–20 mitoses/2 mm² and/or Ki67 3–20%), and high-grade G3 NETs (>20 mitoses/2 mm² and/or Ki67 > 20%) (3). Surgical resection of the primary tumor and locoregional lymph nodes is recommended for patients with localized or locoregional disease and remains the only curative treatment option for patients with GEP-NENs (2). Patients with metastatic disease are generally treated with systemic therapy. One such systemic treatment is peptide receptor radionuclide therapy (PRRT), used for NETs that express somatostatin receptors (SSTRs). PRRT is typically considered a second-line option for patients with progressive NETs following treatment with non-radioactive somatostatin analogs (SSA).

Clinical evidence supporting the efficacy of PRRT in tumor control has been provided by the phase 3 NETTER-1 and NETTER-2 studies. The NETTER-1 trial was a randomized, controlled, phase 3 study comparing four cycles of 7.4 GBq of [¹⁷⁷Lu]Lu-DOTA-TATE (administered every 8 weeks) combined with standard-dose long-acting octreotide (30 mg) intramuscularly every 4 weeks, versus a control group receiving high-dose long-acting octreotide (60 mg) every 4 weeks. The study population included patients with somatostatin receptor-positive, advanced, grade 1 or 2 midgut NETs showing progression under treatment with octreotide LAR (20-30 mg every 3-4 weeks). The estimated progression-free survival (PFS) rate at 20 months was 65.2% in the [¹⁷⁷Lu]Lu-DOTA-TATE group versus 10.8% in the control group. The objective response rate (ORR) was significantly higher in the [¹⁷⁷Lu]Lu-DOTA-TATE group (18%) compared to the control group (3%) (4). In the final overall survival (OS) analysis, with a median follow-up of over 6.3

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years in each group, the median OS was 48.0 months in the [¹⁷⁷Lu]Lu-DOTA-TATE group, with no statistically significant difference compared to the control group (36.3 months), due to crossover to PRRT in the control arm (5).

The NETTER-2 trial was a randomized, parallel-group, phase 3 study comparing four cycles (every 8 ± 1 weeks) of [¹⁷⁷Lu]Lu-DOTA-TATE combined with octreotide long-acting repeatable (LAR) 30 mg intramuscularly, followed by maintenance octreotide LAR 30 mg every 4 weeks ([¹⁷⁷Lu]Lu-DOTA-TATE group), versus a control group receiving high-dose octreotide LAR 60 mg every 4 weeks. The patients included were newly diagnosed with somatostatin receptor-positive, advanced GEP-NETs of high-grade 2 (Ki67 $\geq 10\%$ and $\leq 20\%$) or grade 3 (Ki67 $> 20\%$ and $\leq 55\%$). The median PFS was 22.8 months in the [¹⁷⁷Lu]Lu-DOTA-TATE group versus 8.5 months in the control group. The ORR was also significantly higher in the [¹⁷⁷Lu]Lu-DOTA-TATE group (43%) compared to the control group (9.3%). OS data were still immature at the time of the primary PFS analysis. Long-term follow-up is ongoing, and OS will be assessed during the final analysis (6). Findings from the NETTER-2 study indicate that PRRT may play a promising role as a first-line therapy in NETs.

Following the NETTER-1 and NETTER-2 studies, a third trial, NETTER-3 (NCT06784752), is currently ongoing. This Phase 3, multicenter, randomized, open-label study aims to assess the efficacy and safety of [¹⁷⁷Lu]Lu-DOTA-TATE in combination with long-acting octreotide compared to octreotide LAR alone in newly diagnosed patients with SSTR-positive, well-differentiated grade 1 and grade 2 (Ki-67 $< 10\%$) advanced GEP-NETs presenting with high disease burden.

PRRT is endorsed by the European Neuroendocrine Tumor Society (ENETS) consensus guidelines as an effective option for inoperable locoregional or distant metastatic NETs with sufficient somatostatin receptor expression, preferably documented by PET/CT (7). With increasing tumor proliferation (Ki-67), somatostatin receptor expression and uptake on SSTR-based imaging decline, whereas [18F]FDG PET/CT uptake typically rises. Consequently, [18F]FDG PET/CT is often preferred for detecting higher-grade NETs and NECs, while both imaging modalities provide complementary information (8). Assessing concordance between SSTR-positive lesions and those with a glycolytic phenotype is central to patient selection and reflects the theranostic principle underlying PRRT, combining imaging and therapy in tumors expressing somatostatin receptors. The guidelines identify [¹⁷⁷Lu]Lu-DOTA-TATE as the reference agent, usually delivered in four cycles with concurrent renal protection using amino-acid infusion containing lysine and arginine. Standard pre-treatment assessment and monitoring should include hematology, renal and hepatic function tests. Reported

toxicities are generally modest (nausea, vomiting, abdominal pain, temporary mild hair loss, transient hematological suppression), though a small long-term risk of myelodysplastic syndrome or leukaemia exists; therefore, serial blood monitoring and structured long-term follow-up, including imaging and quality-of-life assessments, are advised (7).

PRRT is reimbursed in Belgium with both magistral (since 01/01/2022) and commercial (since 01/09/2022; Lutathera®) preparations for patients with unresectable or metastatic, progressive NETs with Ki-67 $< 55\%$. Eligibility requires disease progression under non-radioactive SSA, SSTR overexpression on PET/CT (uptake greater than liver), adequate organ function, life expectancy over 6 months, and absence of pregnancy, lactation, or uncontrolled cardiac failure. PRRT is administered intravenously by a nuclear medicine specialist authorized by the Federal Agency for Nuclear Control (FANC).

The objective of the present study is to evaluate the efficacy and safety of [¹⁷⁷Lu]Lu-DOTA-TATE in patients with GEP-NETs treated under real-life conditions at the Institut Jules Bordet (IJB) over a 10-year period (2013–2023), and to identify prognostic factors potentially associated with prolonged PFS and OS. IJB is a tertiary referral center in Belgium, having the ENETS Center of Excellence (CoE) qualification (ULB NET Center).

Methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional Ethics Committee (CE3974). It is a single-center retrospective analysis including GEP-NET patients who received at least one cycle of treatment with [¹⁷⁷Lu]Lu-DOTA-TATE at IJB from July 23, 2013 to July 23, 2023. Eligibility criteria for PRRT comprised histologically confirmed, unresectable, metastatic NETs with documented progression and sufficient SSTR expression on pre-therapeutic SSTR imaging (tumor uptake higher than physiological liver uptake on [68Ga]Ga-DOTA-TATE PET/CT) with no discordant (FDG positive/ SSTR negative) lesions. Additional inclusion criteria for PRRT were a glomerular filtration rate (GFR) above 30 ml/min/1.73 m², a leukocyte count equal to or greater than $2 \times 10^9/L$, and a platelet count above $70 \times 10^9/L$. This study included only patients whose histological reports were complete and documented the Ki-67 index.

The standard therapeutic regimen consisted of four fixed-activity cycles of 7.4 ($\pm 10\%$) GBq of [¹⁷⁷Lu]Lu-DOTA-TATE, administered at 10–12-week intervals. In the event of clinically significant toxicity, this interval could be extended up to 16 weeks. In the context of retreatment (PRRT-2 and PRRT-3), 2 to 4 additional cycles of [¹⁷⁷Lu]Lu-DOTA-TATE were administered at intervals of 10 to 12 weeks. In patients requiring ongoing SSA therapy for hormonal syndromes, long-acting SSAs

were withheld 4-6 weeks before PRRT or replaced by short-acting SSAs paused 48 hours prior and resumed 24 hours after [¹⁷⁷Lu]Lu-DOTA-TATE administration. Renal protection was provided through an amino acid infusion (Proteinsteril Hepa 8%, Fresenius Kabi), administered over 4 hours, starting 30 minutes prior to PRRT administration. Intravenous antiemetic treatment was given 30 minutes before the amino acid infusion.

Patients underwent follow-up consultations during treatment (between cycles) and after treatment (mainly every 3 to 6 months). Patients were systematically monitored with a complete blood count and assessment of renal and liver function (approximately 5–6 weeks after each [¹⁷⁷Lu]Lu-DOTA-TATE administration and within 3 weeks prior to the next administration). Morphological evaluation by computed tomography (CT) or magnetic resonance imaging (MRI), was generally performed before each PRRT injection, 2-3 months after treatment completion and every 2-3 months until disease progression. In case of suspicion of disease recurrence, a [⁶⁸Ga]Ga-DOTA-TATE PET/CT was performed.

Progression-Free Survival and Overall Survival Analysis

Progression was defined radiologically according to RECIST 1.1 criteria on MRI or CT, or clinically by a sustained increase (>2 weeks) of at least 50% in the frequency of symptoms related to hormone hypersecretion specific to NETs, or an increase by one grade in symptom severity.

Progression-Free Survival (PFS) was defined as the time from the first day of PRRT treatment to progression (radiologic according to RECIST 1.1 or clinical) or death from any cause. Patients who did not exhibit progression according to RECIST 1.1 (stable disease on CT or MRI) but were found to have progression on [¹⁸F]FDG PET/CT or demonstrated increased SSTR-positive tumor burden or new lesions on [⁶⁸Ga]Ga-DOTA-TATE PET/CT - and for whom this led to the initiation of a new treatment - were censored at the date of that new treatment's start.

Overall Survival (OS) was calculated from the first day of PRRT treatment until death. For OS and PFS, patients without an event were censored at the date of last contact.

Adverse Events Assessment

All adverse events occurring from the start of treatment up to 9-10 weeks after the last PRRT cycle were collected and graded according to version 5 of the Common Terminology Criteria for Adverse Events (CTCAE v5) (9). Beyond the 10th post-treatment week, only data on the date of progression, vital status, and the occurrence of hematologic malignancies were collected.

For anemia, leukopenia, lymphopenia, and thrombocytopenia, baseline grades were also recorded

to account for pre-existing hematologic abnormalities. Consequently, the delta highest grade of hematologic toxicity was defined as: Δ highest grade = highest grade – baseline grade (10).

Renal function was assessed using the estimated GFR (eGFR) based on the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). For liver function, levels of gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were analyzed at baseline, during treatment, and after treatment. For hypoalbuminemia, the delta highest grade was determined.

Statistical Analysis

Kaplan-Meier analyses were used to estimate survival probabilities (PFS and OS). Univariate and multivariate analyses were conducted to identify factors associated with clinical outcomes (PFS, OS). Variables with a p-value < 0.1 in the univariate analysis were included in the multivariate analysis. In the multivariate model, a variable was considered a significant prognostic factor for PFS/OS when the p-value was < 0.05. Survival comparisons between subgroups were performed using the log-rank test. Hazard ratios between subgroups were estimated using Cox proportional hazards models. Treatment safety profiles were reported descriptively.

Results

We identified 117 patients with GEP-NETs who were treated with PRRT at IJB between 2013 and 2023. Three patients were excluded from the study due to incomplete histological data. Among the 114 patients with GEP-NETs who were included in the study: 110 were PRRT-naïve (they received their first PRRT or PRRT-1 at IJB), 17 patients received a second PRRT (PRRT-2) at IJB (including 14 who were initially treated at IJB and 3 who had received PRRT-1 at another center), and 2 patients received a third PRRT (PRRT-3) at IJB, one of whom had been treated at another center before arriving at IJB. Patient selection and inclusion is detailed in Figure 1.

PRRT-1

A total of 110 patients with GEP-NETs (61 women and 49 men) received at least one cycle of initial PRRT at IJB during the study period. Of these, 37 patients were managed within the prospective phase 2 LuMEN trial (NCT01842165).

Baseline clinical and histopathological characteristics are summarized in Table 1.

Among the 110 patients, 65 (59.1%) completed all four cycles, 20 (18.2%) completed three cycles, 12 (10.9%) completed two cycles, and 10 (9.1%) received only one cycle. Three patients (2.7%) received five cycles.

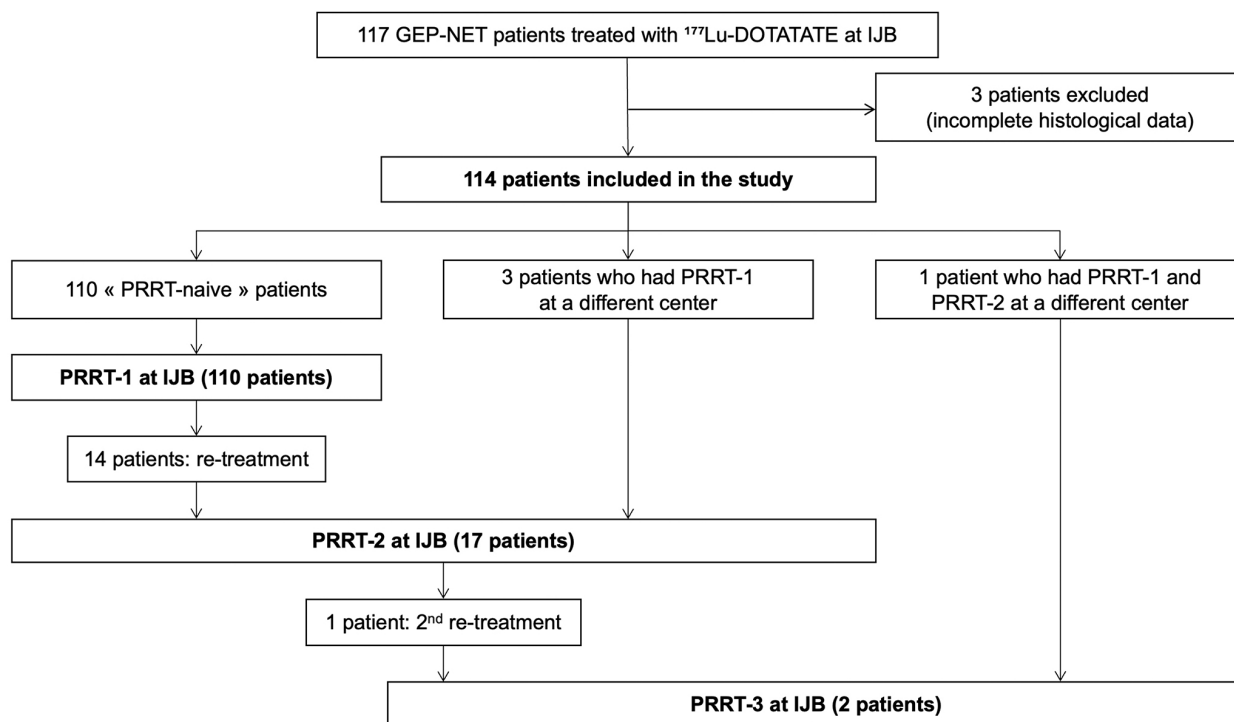


Figure 1

Reasons for not completing the standard four-cycle protocol included: radiologic progression during PRRT-1 in 8 patients, significant myelotoxicity in 3 patients, clinical deterioration in 9 patients, death unrelated to PRRT in 8 patients, significant partial response after 2 or 3 cycles (leading to significant decrease in SSTR expression on PET imaging) in 7 patients, and patient decision or loss to follow-up in 7 patients.

RECIST 1.1 Response Assessment

Radiologic response assessment according to RECIST 1.1 at the end of treatment was available for 102 patients. Among them, a complete response (CR) was observed in 1% (n = 1), a partial response (PR) in 21.6% (n = 22), stable disease (SD) in 60.8% (n = 62), and progressive disease (PD) in 16.7% (n = 17). The objective response rate (ORR) following PRRT-1 was 22.5%, the disease control rate (DCR) was 83.3%.

Survival Data

Median PFS following PRRT-1 was 22.5 months (95% CI, 19.7–29.0) (Figure 2A) and median OS 42.3 months (95% CI, 34.3–55.0) (Figure 2B). Median time of follow-up post PRRT-1 administration was 26.4 months (range: 0.8 – 106.4).

Adverse Events

The most common adverse events (AEs) are summarized in Table 2. Fatigue occurred in 81 patients (73.6%, including one grade 3 case) and alopecia

(low grade and transient) in 50 patients (45.5%). Gastrointestinal AEs included nausea (n = 41, 37.3%; with one grade 3 case), vomiting (n = 16, 14.5%; with one grade 3 case), abdominal pain (n = 54, 49.1%; with 7 grade 3 cases), sub-occlusive episodes (n = 4), bowel obstruction (n = 2), and one case of acute pancreatitis in a patient with pancreatic metastases. Diarrhea was reported by 63 patients (57.3%). Among them, 10 patients (15.9%) reported a single episode of watery diarrhea, 9 patients (14.3%) had transient watery diarrhea within the first few days following PRRT administration, and 44 other patients (69.8%) already had pre-existing chronic watery diarrhea before treatment.

Among 107 patients with available post-treatment laboratory data, lymphopenia was the most frequent toxicity, with grade 3 in 50 patients (46.7%) and grade 4 in 4 (3.7%). Anemia, thrombocytopenia, and leukopenia were mainly grade 1 or 2. Grade 3 events included anemia (n = 2, 1.9%), thrombocytopenia (n = 2, 1.9%), and leukopenia (n = 3, 2.8%). One grade 4 event was observed, corresponding to a case of thrombocytopenia (0.9%). Distribution of Δ highest grade is shown in Table 3.

Myelodysplastic syndrome (MDS) was observed in 2 patients. The first case was diagnosed during PRRT treatment (shortly after the first cycle) and, after discussion with hematologists, was considered unrelated to PRRT. In the second case, the time between the first PRRT cycle and the definitive MDS diagnosis was 31 months. In this patient, MDS with multilineage dysplasia was confirmed by bone marrow biopsy and was considered related to PRRT.

Table 1. — Clinical and histopathological characteristics.

Characteristics	Number of patients (%)
Gender	
Male	49 (44.5%)
Female	61 (55.5%)
Tumor grade	
Grade 1	38 (34.5%)
Grade 2	62 (56.4%)
Grade 3	10 (9.1%)
Primary tumor site	
Small intestine	63 (57.3%)
Pancreas	34 (30.9%)
Colon or rectum	11 (10%)
Stomach	2 (1.8%)
Functional activity	
Functional	47 (42.7%)
Non-functional	63 (57.3%)
Sites of metastasis	
Liver	102 (92.7%)
Lymph node	90 (81.8%)
Bone	62 (56.4%)
Peritoneum	37 (33.6%)
Lung or/and pleura	15 (13.6%)
Pancreas	9 (8.2%)
Subcutaneous	5 (4.5%)
Muscle	4 (3.6%)
Adrenal gland	4 (3.6%)
Spleen	3 (2.7%)
Breast	3 (2.7%)
Ovary	3 (2.7%)
Heart/ pericardium	3 (2.7%)
Retro-orbital	2 (1.8%)
Meninx	1 (0.9%)
Treatment	
Somatostatin analogs	101 (91.8%)
Surgery	77 (70.0%)
Chemotherapy	30 (27.3%)
Radiotherapy	19 (17.3%)
Embolization	26 (23.6%)
¹³¹ I-MIBG	1 (0.9%)
Everolimus	30 (27.3%)
Radiofrequency ablation	7 (6.4%)
Interferon alpha	1 (0.9%)
Sunitinib	11 (10.0%)
Number of treatment modalities before ¹⁷⁷Lu-DOTATATE	
≤ 2	56 (50.9%)
3	28 (25.5%)
4	14 (12.7%)
≥ 5	12 (10.9%)

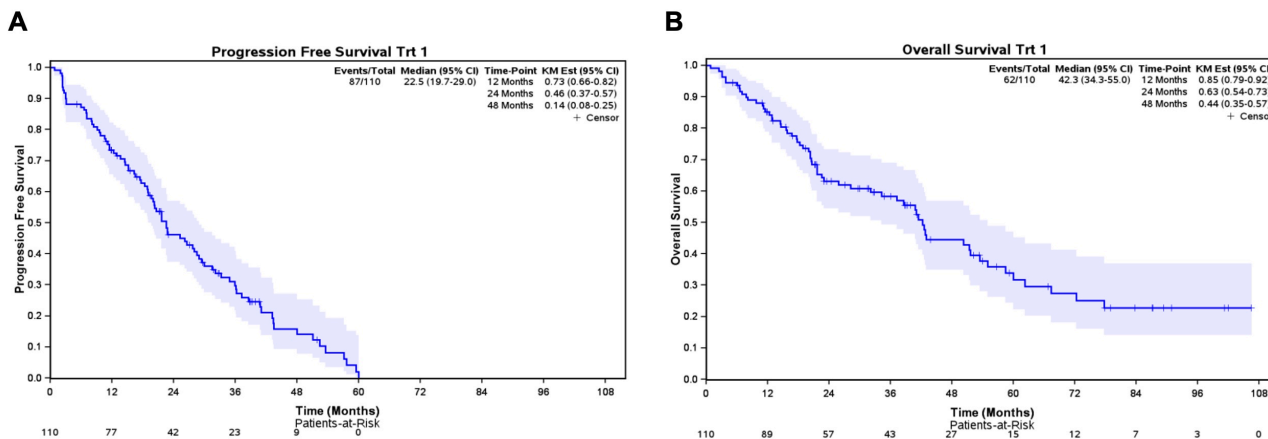


Figure 2A-B

Table 2. — Most common adverse events (>10% of the patients).

	Any grade, n (%)	Grade 3, n (%)
Hematological toxicity (total n = 107)		
Lymphopenia	92 (86%)	54 (50.5%)
Thrombocytopenia	53 (49.5%)	3 (2.8%)
Anemia	43 (40.2%)	2 (1.9%)
Leucopenia	34 (31.8%)	3 (2.8%)
Hepatic toxicity (total n = 105)		
AST increase	29 (27.6%)	-
ALT increase	27 (25.7%)	-
GGT increase	23 (21.9%)	1 (1.0%)
Other (total n = 110)		
Fatigue	81 (73.6%)	1 (0.9%)
Diarrhea	63 (57.3%)	1 (0.9%)
Abdominal pain	54 (49.1%)	7 (6.4%)
Alopecia	50 (45.5%)	-
Nausea	41 (37.3%)	1 (0.9%)
Flush	24 (21.8%)	-
Weight loss	19 (17.3%)	-
Vomiting	16 (14.5%)	1 (0.9%)
Inappetence	14 (12.7%)	-

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase.

Renal toxicity \geq grade 3 was rare and occurred in patients with pre-existing renal impairment and risk factors (hypertension, diabetes, age >70 years). Hepatic toxicity mainly consisted of transient increases in liver enzymes (as demonstrated in Table 2). Moreover, seven patients showed elevated bilirubin levels (n = 7, 6.7%), including 2 cases with grade 3 elevation (1.9%). A decrease in albumin levels was reported in 9 patients: the Δ highest grade was 1 in 6 of them, and 2 in the remaining 3.

Analysis of Potential Prognostic Factors

In the univariate Cox regression analysis, the following factors were statistically significant in

predicting PFS: histological grade, chromogranin A (CgA) level, alkaline phosphatase (ALP) level, sodium level, albumin level, FDG avidity, and the number of treatments received prior to PRRT. Complete data for all these parameters were available for 99 patients, allowing their inclusion in the multivariate model. In the multivariate analysis, only histological grade, CgA level, sodium level, and albumin level remained significant (Table 4). Kaplan–Meier curves for PFS in selected cohorts are shown in Figure 3.

In the univariate Cox regression analysis, the following factors were statistically significant in predicting OS: CgA level, ALP level, neutrophil-to-lymphocyte ratio (NLR), and albumin level. In multivariate analysis, only

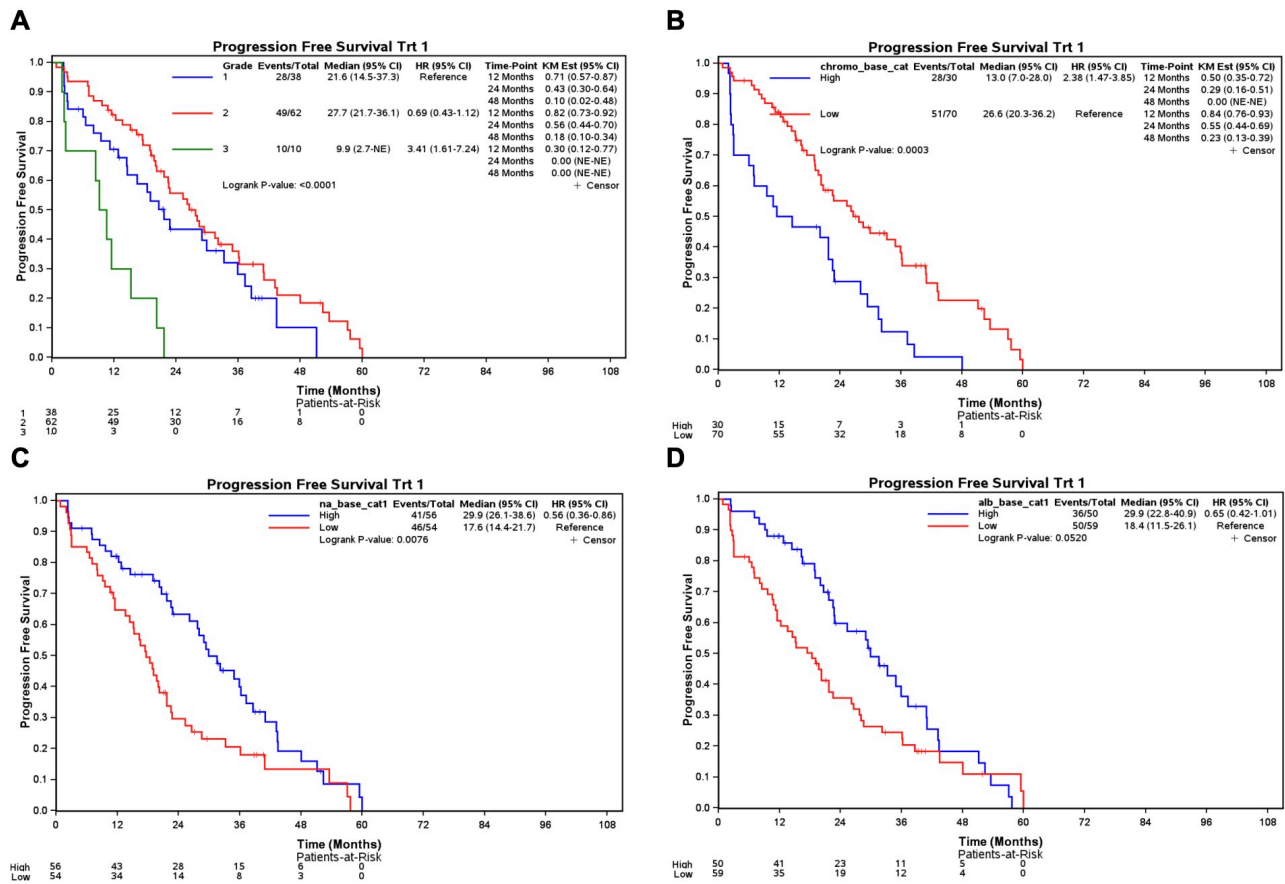


Figure 3A-B-C-D

Table 3. — Distribution of Δ highest grade of hematological toxicities.

	Δ highest grade				Total
	1	2	3	4	
Lymphopenia	27 (29.3%)	32 (34.8%)	32 (34.8%)	1 (1.1%)	92
Thrombocytopenia	44 (83%)	6 (11.3%)	3 (5.7%)	0 (0%)	53
Anemia	38 (88.4%)	5 (11.6%)	0 (0%)	0 (0%)	43
Leucopenia	13 (38.2%)	18 (52.9%)	3 (8.8%)	0 (0%)	34

CgA level, NLR, and albumin level remained significant (Table 5). Kaplan–Meier curves for OS in selected cohorts are shown in Figure 4.

PRRT-2

A total of 17 patients received their second treatment with PRRT at IJB between 23/07/2013 and 23/07/2023. Of these, 5 patients received 4 cycles, 3 patients received 3 cycles, 7 patients received 2 cycles, and 2 patients received only one cycle of PRRT-2.

Radiological response according to RECIST 1.1 at the end of PRRT-2 was available for 13 patients. Among them, a partial response (PR) was observed in 38.5% (n = 5), stable disease (SD) in 38.5% (n = 5), and progressive disease (PD) in 23% (n = 3).

The estimated median PFS for the patients treated with PRRT-2 (n = 17) was 12.2 months (95% CI, 11.3–NE)

(Figure 5A). The estimated median OS following PRRT-2 was 28.2 months (95% CI, 16.3–NE) (Figure 5B). Median time of follow-up post PRRT-2 administration was 27 months (range: 2.2 – 58.1).

PRRT-3

Two patients received a third treatment with PRRT between 23/07/2013 and 23/07/2023. The first patient experienced disease progression according to RECIST 1.1 after 2 cycles of PRRT-3. The second patient received 4 cycles of PRRT-3, resulting in disease stabilization.

Discussion

The results of this retrospective analysis are overall consistent with previously published data and confirm the overall efficacy and safety of ¹⁷⁷Lu-PRRT

Table 4. — Analysis of potential prognostic factors for progression-free survival (PFS).

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Grade		<.0001		0.0027
1	Reference		Reference	
2	0.69 (0.43-1.12)	0.1313	0.69 (0.40-1.18)	0.1727
3	3.41 (1.61-7.24)	0.0014	2.75 (1.21-6.27)	0.0162
Primary tumor site		0.2673		
Small intestine	Reference			
Pancreas	1.46 (0.92-2.33)	0.1091		
Colon or rectum	0.93 (0.44-1.98)	0.8506		
Stomach	2.35 (0.57-9.77)	0.2391		
Functional activity		0.9135		
Non-functional	Reference			
Functional	1.02 (0.67-1.57)	0.9135		
Chromogranin A		0.0004		0.0010
< 1000 µg/L	Reference		Reference	
≥ 1000 µg/L	2.38 (1.47-3.85)	0.0004	2.57 (1.46-4.51)	0.0010
Alkaline phosphatase		<.0001		0.1459
< 130 UI/L	Reference		Reference	
≥ 130 UI/L	2.51 (1.59-3.94)	<.0001	1.51 (0.87-2.63)	0.1459
Sodium	0.86 (0.79-0.94)	0.0005	0.84 (0.75-0.93)	0.0008
Albumin	0.93 (0.87-0.99)	0.0162	0.93 (0.86-0.99)	0.0275
NLR	1.07 (0.99-1.16)	0.0775	1.01 (0.90-1.12)	0.9230
¹⁸F-FDG PET status		0.0305		0.1805
Negative	Reference		Reference	
Positive	1.77 (1.06-2.97)	0.0305	1.54 (0.82-2.89)	0.1805
Number of treatment modalities before PRRT		0.0304		0.7164
≤ 3	Reference		Reference	
> 3	1.72 (1.05-2.82)	0.0304	1.11 (0.62-1.98)	0.7164

HR: hazard ratio; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; ¹⁸F-FDG PET: ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography; PRRT: peptide receptor radionuclide therapy.

as performed in a Belgian ENETS accredited Center of Excellence. In terms of efficacy, in our cohort of patients, the median PFS following PRRT-1 was 22.5 months, which is broadly comparable to that observed in the NETTER-2 study (22.8 months) (6), although slightly lower than the medians reported by Ezziddin et al. (26 months) (11), Brabander et al. (29 months) (12), and Alsadik et al. (33 months) (13). The median OS following PRRT-1 in our study was 42.3 months, which is lower than that reported in NETTER-1 (48 month) (5), by Brabander et al. (63 months) (12) and Ezziddin et al. (55 months) (11). This difference may be partially explained by the higher proportion of grade 3 tumors in our cohort (9.1%) compared to other previously mentioned studies (≤5%) (5, 11, 12, 13). Additionally, regarding metastatic sites, we observed a high rate of liver metastases (92.7%), slightly higher than in the reference studies. The proportion of bone metastases

in our cohort was among the highest reported across published series.

The objective response rate (ORR) following PRRT-1 reached 22.5%, consistent with the NETTER-1 data (18%) (4) and similar to that reported by Alsadik et al. (22%) (13). The disease control rate (DCR), estimated at 83.3%, aligns with literature values (around 80–90%) (6,11,12,13).

The AEs most frequently reported by the patients included in our study were fatigue, diarrhea, abdominal pain, alopecia, and nausea. In comparison, the most common adverse events in the NETTER-1 trial were nausea (59%), vomiting (47%), fatigue (40%), diarrhea (29%), and abdominal pain (26%) (4). In the NETTER-2 study, nausea (27%), diarrhea (26%), and abdominal pain (18%) were most commonly reported (6). Nausea and vomiting were primarily attributable to amino acid infusions rather than to PRRT itself. In our study, four

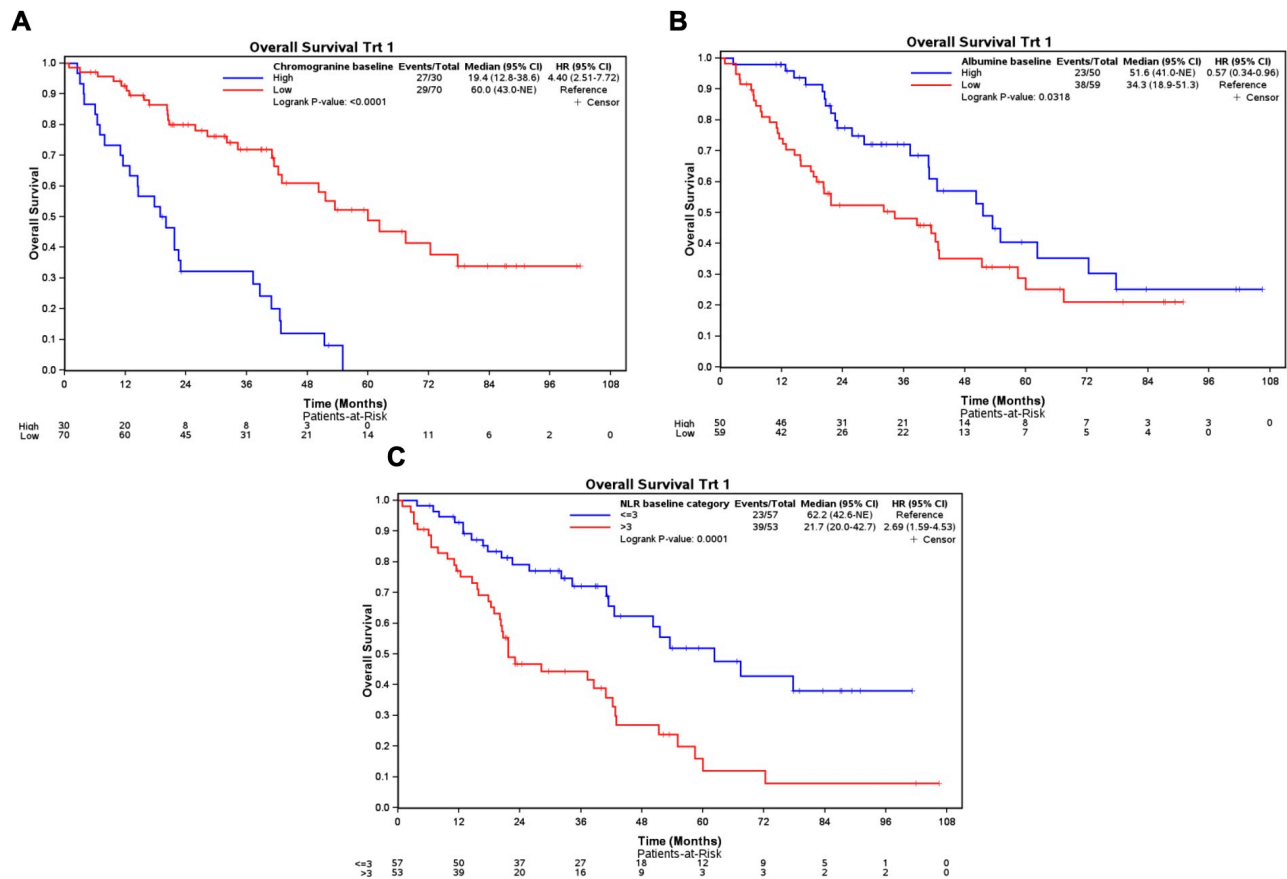


Figure 4A-B-C

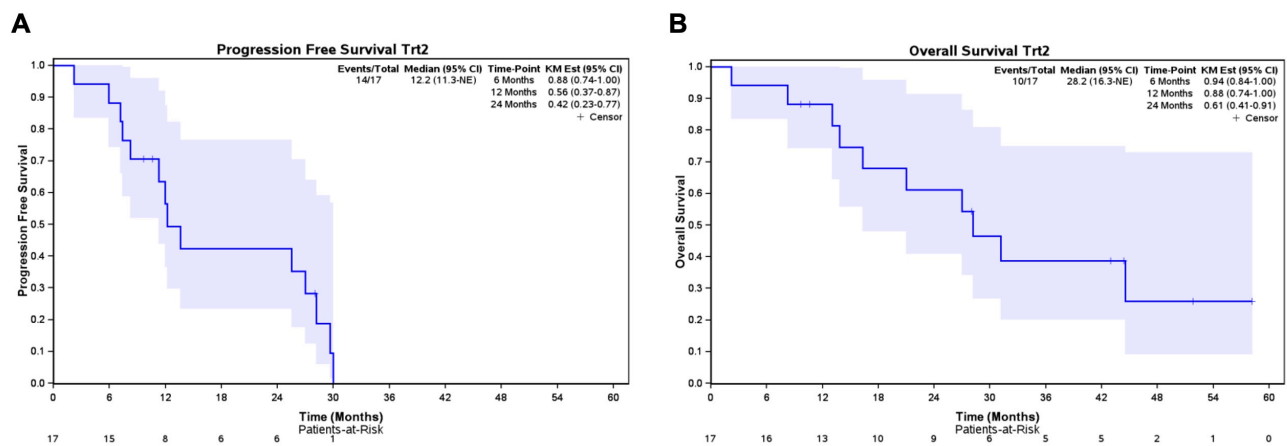


Figure 5A-B

patients developed sub-occlusive intestinal syndrome, and two developed bowel obstruction after [¹⁷⁷Lu]Lu-DOTA-TATE exposure. This complication may result from post-radiation inflammation and fibrosis, particularly in patients carrying large mesenteric or peritoneal lesions. Corticosteroids may help reduce inflammation, though their preventive effect remains unclear (14). One patient with pancreatic metastases developed grade 3 acute pancreatitis, due to tumor irradiation causing peritumoral inflammation and edema, leading to secondary pancreatic duct obstruction (15).

In our cohort, the hematologic toxicity profile was generally comparable to previous series, with only few patients experiencing transient grade 3–4 hematologic toxicities (<10%), except for lymphopenia. The rate of transient grade 3–4 lymphopenia was high in our cohort (50.5%), similar to that reported by Brabander (50%) (12), but higher than in the NETTER-1 study, where only 9% of patients treated with ¹⁷⁷Lu-PRRT developed grade 3–4 lymphopenia (4). Although lymphocytes — particularly B cells — are known to be radiosensitive, and lymphopenia is a common finding during PRRT, therapy modification is usually unnecessary, as

Table 5. — Analysis of potential prognostic factors for overall survival (OS).

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Grade		0.1292		
1	Reference			
2	0.72 (0.42-1.25)	0.2430		
3	1.61 (0.68-3.81)	0.2785		
Primary tumor site		0.6099		
Small intestine	Reference			
Pancreas	0.83 (0.48-1.45)	0.5186		
Colon or rectum	0.55 (0.20-1.55)	0.2571		
Stomach	0.50 (0.07-3.66)	0.4925		
Functional activity		0.1181		
Non-functional	Reference			
Functional	1.49 (0.90-2.46)	0.1181		
Chromogranin A		<.0001		<.0001
< 1000 µg/L	Reference		Reference	
≥ 1000 µg/L	4.40 (2.51-7.72)	<.0001	4.28 (2.31-7.95)	<.0001
Alkaline phosphatase		0.0013		0.1027
< 130 UI/L	Reference		Reference	
≥ 130 UI/L	2.30 (1.39-3.82)	0.0013	1.62 (0.91-2.88)	0.1027
Sodium	0.91 (0.83-1.01)	0.0720	0.89 (0.80-1.00)	0.0517
Albumin	0.88 (0.82-0.94)	0.0001	0.89 (0.82-0.96)	0.0026
NLR	1.14 (1.07-1.22)	<.0001	1.13 (1.04-1.23)	0.0035
18F-FDG PET status		0.3185		
Negative	Reference			
Positive	1.34 (0.76-2.36)	0.3185		
Number of treatment modalities before PRRT		0.2261		
≤ 3	Reference			
> 3	1.40 (0.81-2.43)	0.2261		

HR: hazard ratio; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; 18F-FDG PET: 18F-Fluorodeoxyglucose Positron Emission Tomography; PRRT: peptide receptor radionuclide therapy.

infectious or opportunistic complications are uncommon (10). The occurrence of myelodysplastic syndrome in our cohort (1.8%) is consistent with the rates reported in NETTER-1 (2%) and by Brabander et al. (1.5%) (4,12).

Grade 3–4 renal toxicity was observed in two patients, both of whom had impaired renal function prior to PRRT. Similarly, a low incidence of severe renal toxicity has been reported in other studies (6, 13). Grade 3–4 hepatic toxicity remains a rare adverse event across published data (6,12).

Tumor grade, primarily determined by the Ki-67 proliferation index, is an important prognostic factor in NET patients treated with PRRT. In our study, G3 was significantly associated with a shorter PFS. In the study by Pencharz et al., a higher tumor grade was significantly associated with lower PFS (16). Another study of 1,048 NEN patients treated with PRRT demonstrated that tumor grade was significantly

associated with shorter PFS only in patients with G3 tumors, with no significant differences between grade 1 and grade 2 tumors (17). Similar findings were reported by Katona et al., where the only significant difference was seen in the G3 group, which had shorter OS and PFS compared to other groups (18).

Chromogranin A may be elevated in several non-tumor conditions (e.g., gastritis, proton pump inhibitor treatment, hypertension, renal and hepatic failure, pancreatitis) as well as in non-neuroendocrine tumors such as prostate cancer or differentiated thyroid cancer (19). In NENs, CgA levels depend on the tumor's site of origin, on tumor burden and secretory activity. SSA treatment also influences CgA levels, complicating its reliability as a tumor mass marker in SSA-treated patients. Nonetheless, CgA's role in the management and follow-up of NEN patients has been reported in several studies (20). A study of 782 NET patients treated with

PRRT found that a CgA level >336 µg/L was associated with reduced PFS, and levels >112 µg/L with shorter OS (21). In a North American cohort analysis, pre-PRRT CgA levels >3 times the upper limit of normal (ULN) were associated with increased mortality risk (22). In our study, CgA level was associated with both PFS and OS.

In a retrospective analysis of 649 NEN patients treated with [¹⁷⁷Lu]Lu-DOTA-TATE PRRT, Refardt et al. found that hyponatremia (serum sodium < 135 mmol/L) was associated with reduced OS compared with normonatremia. However, no significant association with PFS was observed (23). Conversely, in our study, sodium level was a prognostic factor for PFS but not OS.

Hypoalbuminemia may reflect systemic inflammation, malnutrition, or liver involvement — all associated with poor prognosis. In our analysis, a baseline albumin level was identified as a prognostic factor for PFS and OS. A retrospective study conducted by Papantoniou et al. on 557 NET patients treated with PRRT demonstrated that lower albumin was associated with shorter median OS (24). Albumin is a key component of inflammation-related prognostic scores, such as the Inflammation-Based Index (IBI), which relies on serum C-reactive protein (CRP) and albumin levels. According to Black et al., higher pre-treatment IBI scores (i.e. CRP > 10 mg/L and/or albumin < 35 g/L) are associated with poorer OS and PFS in PRRT-treated patients (25).

The NLR, calculated as the ratio of total neutrophils to lymphocytes, is a biomarker of systemic inflammation. In our study, it was identified as a prognostic factor for OS. According to previous studies, various NLR thresholds have been associated with poorer surgical outcomes, reduced response to chemotherapy and radiotherapy, shorter PFS, and worse OS in different cancer types (26). De Lima et al., in a study involving 96 NET patients undergoing PRRT, reported that patients with high pre-therapy NLR had a significantly shorter OS and a trend toward a shorter PFS (27). However, in a larger cohort (557 PRRT-treated patients), the derived NLR (dNLR) was not significantly associated with OS in the analysis adjusted for age, CgA, performance status, Ki-67, tumor site and number of prior treatment lines (24).

Most of the available evidence on retreatment with PRRT in NETs derives from retrospective cohort studies, with prospective randomized data still lacking. The NET RETREAT trial (NCT05773274) is a randomized phase 2 study designed to address this gap. It compares [¹⁷⁷Lu]Lu-DOTA-TATE retreatment with standard targeted therapies (everolimus, sunitinib for pancreatic NETs, or cabozantinib in the US) in patients with metastatic/unresectable GEP-NETs who have progressed following previous PRRT.

In our study, median PFS after PRRT-2 was 12.2 months and median OS was 28.2 months. In the

retrospective analysis by Kashyap et al. involving 63 GEP-NET patients, PFS after retreatment with PRRT was 19 months (28). According to Strosberg, pooled median PFS from a random-effects meta-analysis in patients who received both initial and retreatment PRRT with [¹⁷⁷Lu]Lu-DOTA-TATE (N = 5 studies, 272 patients) was 12.26 months (following PRRT-2). In a random-effects meta-analysis (N = 2 studies, 194 patients) including those initially treated with either [¹⁷⁷Lu]Lu-DOTA-TATE or 90Y-PRRT followed by [¹⁷⁷Lu]Lu-DOTA-TATE retreatment, pooled median OS was estimated at 26.78 months. However, interpretation of OS data following retreatment PRRT is limited by heterogeneity across studies and the small number of studies reporting analyzable survival outcomes (29).

This study has several limitations. Some information — particularly regarding adverse events or long-term follow-up — may be incomplete or missing. Although morphological assessment was performed according to RECIST 1.1, it was not centrally reviewed, which exposes the study to inter-observer variability. Additional heterogeneity stems from differences in tumor grade, disease burden, prior treatments, and PRRT protocols (including number of cycles and intervals between them). The limited number of included patients may reduce statistical power, particularly for subgroup or prognostic factors analyses. Finally, the monocentric nature of the study, conducted at a tertiary center, may limit the generalizability of the results to other settings.

Conclusions

This retrospective single-center study confirms the efficacy and safety of PRRT in a real-world population of patients with advanced GEP-NETs expressing SSTR treated in a tertiary ENETS CoE hospital. Initial treatment with [¹⁷⁷Lu]Lu-DOTA-TATE (PRRT-1) resulted in DCR of 83.3%, with median PFS of 22.5 months and median OS of 42.3 months. The treatment was generally well tolerated, with relatively few adverse events, grade 3 or 4 renal toxicity observed in less than 2% of patients, and grade 3 or 4 hematological toxicity (excluding lymphopenia) occurring in less than 10% of cases. These real-world post-marketing data are well aligned with data obtained from phase 3 trials.

Declarations

Conflicts of interest: None declared.

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