

Peptide receptor radionuclide therapy in the management of gastrointestinal neuroendocrine tumors: efficacy profile, safety, and quality of life

Stefano Severi¹
Ilaria Grassi¹
Silvia Nicolini¹
Maddalena Sansovini¹
Alberto Bongiovanni²
Giovanni Paganelli¹

¹Nuclear Medicine Unit,
²Osteoncology and Rare Tumors
Center, Istituto Scientifico Romagnolo
per lo Studio e la Cura dei Tumori
(IRST) IRCCS, Meldola, Italy

Abstract: Peptide receptor radionuclide therapy (PRRT), developed over the last two decades, is carried out using radiopharmaceuticals such as ⁹⁰Y-DOTA-Tyr3-octreotide and ¹⁷⁷Lu-DOTA-Tyr3-octreotate (¹⁷⁷Lu-Dotatate). These radiocompounds are obtained by labeling a synthetic somatostatin analog with a β -emitting radioisotope. The compounds differ from each other in terms of their energetic features (due to the radionuclide) and peptide receptor affinity (due to the analog) but share the common characteristic of binding specific membrane somatostatin receptors that are (generally) overexpressed in neuroendocrine neoplasms (NENs) and their metastases. NENs are tumors arising from diffuse neuroendocrine system cells that are classified according to grading based on Ki67 percentage values (Grades 1 and 2 are classed as neuroendocrine tumors [NETs]) and to the anatomical site of occurrence (in this paper, we only deal with gastroenteropancreatic [GEP]-NETs, which account for 60%–70% of all NENs). They are also characterized by specific symptoms such as diarrhea and flushing (30% of cases). Despite substantial experience gained in the area of PRRT and its demonstrable effects in terms of efficacy, safety, and improvement in quality of life, these compounds are still not registered (registration of ¹⁷⁷Lu-Dotatate for the treatment of midgut NETs is expected soon). Thus, PRRT can only be used in experimental protocols. We provide an overview of the work of leading groups with wide-ranging experience and continuity in data publication in the area of GEP-NET PRRT and report our own personal experience of using different dosage schedules based on the presence of kidney and bone marrow risk factors. Our results on the retreatment of patients previously administered ⁹⁰Y-DOTA-Tyr3-octreotide with a low dosage of ¹⁷⁷Lu-Dotatate are also included. A comment on potential future developments of PRRT in GEP-NETs is provided.

Keywords: ⁹⁰Y-Dotatoc, ¹⁷⁷Lu-Dotatate, radiopharmaceutical, radiolabelled receptors, neuroendocrine malignancies, delivered activity

Introduction

Neuroendocrine neoplasms (NENs) are tumors arising from diffuse neuroendocrine system cells and are characterized by high expression of somatostatin receptors (SSTRs) and specific markers, including CgA, synaptophysin, CD53 protein, and the neuron-specific enolase. Given the heterogeneity of these tumors, NEN classification is currently based on the following:

- Grading: leading to classification into well-differentiated tumors or Grade 1 (Ki67 <3%), moderately differentiated tumor or Grade 2 (Ki67 between 3% and 20%), or poorly differentiated tumors or Grade 3 (Ki67 >20%). Grade 1 and 2 tumors are grouped into NETs, while Grade 3 tumors are classed as neuroendocrine carcinomas.^{1,2}

Correspondence: Stefano Severi
Nuclear Medicine Unit, Istituto Scientifico
Romagnolo per lo Studio e la Cura dei
Tumori (IRST) IRCCS, via P. Maroncelli 40,
47014 Meldola (FC), Italy
Tel +39 0543 739 323
Fax +39 0543 739 321
Email stefano.severi@irst.emr.it

- Site of occurrence: although NETs may arise in any body region, 60%–70% originate in the gastroenteropancreatic-NENs (GEP-NENs) tract.

NETs are also characterized by the presence of associated symptoms and as such are considered as functioning tumors (30% of cases). Symptoms relating to hormonal hypersecretion frequently include diarrhea, flushing, right heart failure, and hyper- or hypoglycemia.

Peptide receptor radionuclide therapy (PRRT), developed over the last two decades, is based on the use of a receptor target and represents one of the most effective treatments for well-differentiated unresectable or metastatic NETs. This therapy is performed by labeling a synthetic and stable somatostatin analog with a β -emitting radioisotope. The analog binds specific membrane receptors that are generally overexpressed in NETs and their metastases.³ The complex formed is chemically stable and is internalized into the cell in a favorable position for the irradiation of the nucleus. In addition, the long half-life of the analog allows for a persistent therapeutic effect. The binding mechanism between the somatostatin analog and its receptors has also been used for diagnostic purposes, ie, in scintigraphic exams with ¹¹¹In and ⁶⁸Ga peptide PET.^{4,5}

Historically, the first therapeutic experiences in NETs were performed using ¹¹¹In-pentetreotide and produced a clinical benefit but rarely a radiological response.⁶ Subsequently, a high-energy β emitter, yttrium-90, was evaluated (Emax 2.27 MeV, half-life 64 hours, tissue penetration 7/8 mm). This radioisotope was linked to octreotide, constituting 90Y-DOTA-Tyr3-octreotide (90Y-Dotatoc), a high-energy radiopharmaceutical with good receptor affinity for the SSTR2 peptide. Studies on the use of 90Y-Dotatoc in clinical trials have reported objective response rates in 6%–37% of patients and have shown a positive impact on overall survival (OS), but these trials are highly heterogeneous.^{7–9}

In the mid-2000s, another radiopharmaceutical, ¹⁷⁷Lu-DOTA-Tyr3-octreotate (177Lu-Dotatate), was synthesized. The lower tissue penetration of ¹⁷⁷Lutetium (Emax 0:49 MeV, Rmax 2 mm) is balanced by a longer half-life (6.7 days) of the radionuclide and by the higher peptide receptor affinity (about ninefold higher) for SSTR2s, overexpressed in the majority of NETs. Furthermore, ¹⁷⁷Lutetium has a significant γ emission, which enables good quality posttreatment images to be acquired. These images provide an accurate representation of the distribution of the therapy between all the tumor lesions and can be used to monitor changes in the disease during treatment. The impact of 177Lu-Dotatate PRRT on PFS has been evaluated in numerous papers, with a general consensus reached on its good tolerability, especially for the kidneys, and on its high efficacy.¹⁰ Results obtained in clinical trials with 90Y-Dotatoc and 177Lu-Dotatate have shown good activity and acceptable tolerability¹¹ (Table 1).

Dosimetry studies have confirmed the high specificity of these therapies and their aggressiveness against tumors, together with their ability to spare healthy tissue. Current administration schedules comprise the most appropriate number of cycles (generally four or five) and the best delivery frequency (6 \pm 2 weeks apart). This treatment periodicity allows the patient to recover from the mild side effects of the therapy and increases its effectiveness in terms of the radiobiological activity.¹²

PRRT has proven highly effective in reducing specific symptoms of the neuroendocrine syndrome (diarrhea, bothersome flushing of the face, and cardiac function disorders due to right ventricular dysfunction), which represent a major handicap. PRRT has also proven analgesic efficacy, especially against pain caused by bone metastases that frequently occur in intestinal and bronchial tumors.¹³ The therapy, albeit generally well-tolerated, is not completely free from side effects that can be classified as acute or delayed.¹⁴ The acute

Table 1 Summary of most relevant papers on PRRT in terms of center experience and number of patients treated

Study	Ligand	Number of patients	Tumor origin	Response criteria	OR (%)	SD (%)	DCR	PFS/TTP	Outcome
Imhof et al, ⁷ 2011	90Y-Dotatoc	1,109	NETs	RECIST	34	5.2	39	13 m	OS 23 m
Bushnell et al, ⁸ 2010	90Y-Dotatoc	90	NETs	SWOG	4 (PR)	70	74	16 m	Median OS 26 m
Kwekkeboom et al, ²¹ 2008	177Lu-Dotatate	310	GEP-NETs	SWOG	30	51	19	33 m	Median OS 46 m ^a
Ezziddin et al, ²² 2014	177Lu-Dotatate	68	PNETs	RECIST	60	25	15	34 m	Median OS 53 m
Garkavij et al, ³⁵ 2010	177Lu-Dotatate	12	NETs	RECIST	17 (PR)	57	74	–	–
Swärd et al, ³⁶ 2010	177Lu-Dotatate	26	NETs	RECIST	38	50	88	–	–
Bodei et al, ³⁷ 2011	177Lu-Dotatate	42	NETs	RECIST	31	47	78	36 m	OS 36 m

Note: ^aMedian OS from start of treatment.

Abbreviations: OR, overall response; SD, stable disease; DCR, disease control rate; PFS, progression-free survival; TTP, time-to-progression; PR, partial response; OS, overall survival; m, months; GEP, gastroenteropancreatic; NETs, neuroendocrine tumors; PNETs, pancreatic NETs; RECIST, Response Evaluation Criteria in Solid Tumors; SWOG, Southwest Oncology Group; PRRT, peptide receptor radionuclide therapy; 90Y-Dotatoc, 90Y-DOTA-Tyr3-octreotide; 177Lu-Dotatate, 177Lu-DOTA-Tyr3-octreotate.

side effects, usually mild, are nausea, headache, and, rarely, vomiting; they occur more often in the early postinjection phase and are generally transient. PRRT may exacerbate the neuroendocrine syndrome which, when present, can be treated with symptomatic drugs. The most important delayed side effects are renal and bone marrow toxicity. Renal toxicity is generally avoided or limited by renal protection, which can be obtained with amino acid infusion (arginine or lysine) before and during PRRT. These amino acids, competing with the site of tubular reabsorption of the drug, reduce recirculation of the radioactivity inside the kidneys, thus limiting their exposure. Comparative studies have demonstrated that the competitive action of these amino acids in the kidney is capable of reducing exposure by 39% when coverage of the amino acid lasts for up to 10 hours after administration of the therapy, and by 65% when it lasts for 2 days.^{15,16} Despite substantial experience gained in this area, PRRT radiopharmaceuticals have never been registered and therapy is still only available through the use of experimental protocols. A ¹⁷⁷Lu-Dotatate compound (Lutathera[®], Advanced Accelerator Applications, Saint-Genis-Pouilly, France), which has successfully been tested in midgut NETs, is currently being evaluated for registration.

Generally, patients included in experimental protocols have a positive NET histology and a positive SSTR scintigraphy with ¹¹¹In OctreoScan or ⁶⁸Ga PET-Dota-peptide. A scan is considered positive if lesion uptake is either equal to or greater than liver uptake. Inclusion criteria also generally include objective disease progression, normal blood count (especially adequate hemoglobin, white cell, and platelet count levels) creatinine, and Eastern Cooperative Oncology Group ≤ 2 . Furthermore, a good performance status guarantees patient self-sufficiency and reduces the need for physical assistance during the treatment period (3 days/cycle) spent in a protected hospital environment. Life expectancy is classically set at a minimum of 6 months.

Over time, the use of PRRT, which was created specifically for neuroendocrine tumors, has been extended to other types of confirmed SSTR-positive tumors. Thus, tumors such as non-iodine-absorbing differentiated thyroid cancer, breast cancer, lymphoma, glioma, meningioma, and paraganglioma can be treated with PRRT when registered therapies have failed.

PPRT in GEP-NETs 90Y-Dotatoc

In 2012, an overview on Yttrium-90 Dotatoc therapy in GEP-NETs was published by the Milan group,⁹ in which tolerability,

efficacy, and prospects were discussed. With regard to tolerability, acute side effects were usually mild: fatigue and endocrine syndrome exacerbation were rare and nausea (or more rarely vomiting) was frequently related to amino acid coinfusion. Kidney and bone marrow toxicity were the most important dose-limiting factors. The problem of finding the administered activity threshold was again processed and a role for bioeffective dose (BED) in predicting toxicity speculated. About 40 Gy of BED was indicated as a more likely threshold for renal toxicity by Dale¹⁷ and Barone.¹⁸ All of these authors suggested using a lower BED (28 Gy) threshold if risk factors (ie, long-standing and poorly controlled diabetes and hypertension) were present, and a higher BED (40 Gy) threshold if there were no risk factors.¹⁹ In the study by Bodei et al,¹⁹ the authors defined that the administered dosage and number of cycles administered can effectively contribute to reducing renal and bone marrow dosimetry. In addition, these authors argued that the possible coexistence of unconjugated radionuclides labeling bone in a nonspecific way could increase bone marrow toxicity. In a multicenter study, PRRT with ⁹⁰Y-Dotatoc was shown to induce clinically stable disease (SD) or partial response (PR), according to Southwest Oncology Group (SWOG) criteria, in 74% of patients, leading to a positive impact on survival. PFS was also significantly longer when symptoms such as diarrhea were reduced (Figure 1).⁸ In a Phase I/II study by the Kwekkeboom group,²⁰ 58 patients with GEP-NETs treated with 1.7–32.8 GBq of PRRT reported a clinical benefit in 57% of cases (the true objective response was 20%), with a median OS of 36.7 months.

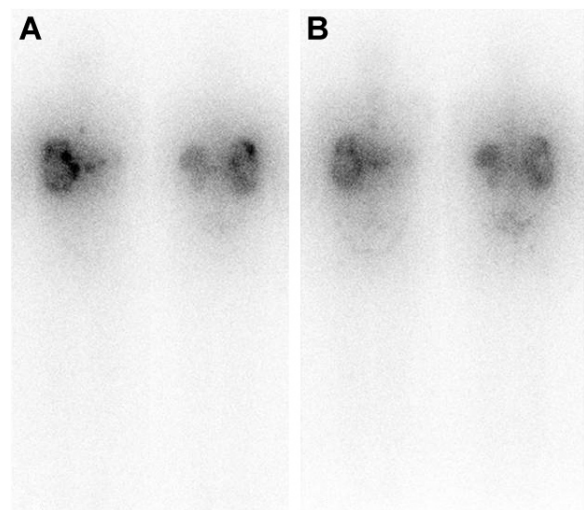


Figure 1 Patient with progressive GEP-NET treated at our institute.

Notes: Total body images acquired after the first (A) and fifth (B) cycle of ⁹⁰Y-Dotatoc. Cumulative activity delivered was 8.14 GBq.

Abbreviations: GEP, gastroenteropancreatic; NET, neuroendocrine tumor; ⁹⁰Y-Dotatoc, ⁹⁰Y-DOTA-Tyr3-octreotide.

¹⁷⁷Lu-Dotatate/Dotatoc

In 2008, the Rotterdam group²¹ was the first to report toxicity and efficacy data on 504 and 310 GEP-NETs patients, respectively, treated with 27.8–29.6 GBq of ¹⁷⁷Lu-Dotatate over a mean of four cycles performed 6/10 weeks apart. Grade 3 or 4 hematological toxicity was present in 3.6% of administrations, with myelodysplastic syndrome in three cases and transient nonfatal liver toxicity in two cases. With regard to efficacy, a complete response was registered in 3% of cases, PR in 28%, and minor response (MR) in 16%. The mean time to progression was 40 months and median OS from diagnosis was 128 months.

The Bonn and Frankfurt (Germany) groups²² retrospectively analyzed 74 metastatic and progressive GEP-NET patients treated with ¹⁷⁷Lu-Dotatate PRRT using 7.9 GBq per cycle over a mean four cycles treatment performed 3 months apart. The median follow-up period was 47 months and data were analyzed using SWOG criteria. Results showed 36.3% PR, 17.6% MR, 35.1% SD, and 10.8% progressive disease (PD). The median PFS was 26 months from the start of treatment and the median OS of the entire cohort was 55 months. In a subgroup of 41 nonpancreatic GEP-NETs, efficacy results showed 22% PR, 17.1% MR, 48.8% SD, and 12.2% PD. Relevant but transient myelosuppression (Grade 3/4; CTCAE 3.0) was reported in less than 10% of cases. No cases of irreversible toxicity, including renal toxicity (Grade 3/4), were reported.

In the past few years, our group in Meldola (Italy) has published a number of papers on Phase II studies focusing on the activity and safety profile of patients treated with ¹⁷⁷Lu-Dotatate.²³ We demonstrated that, as expected, 18-Fluorodeoxyglucose positron emission tomography (FDG PET) was positive in 67% of G2 NET cases, but it was also positive in a large portion of G1 cases (54%). Furthermore, in the same study, FDG PET was found to be an important predictive and prognostic factor. In fact, it was more effective than Ki67 in identifying patients who would respond to PRRT and have a better median PFS. These findings obviously need to be confirmed in larger studies but offer a new and theoretically important option for NET patient stratification.

Our group also carried out a Phase II study of PRRT with ¹⁷⁷Lu-Dotatate in patients with advanced, well-differentiated (G1–G2) gastrointestinal (GI)-NETs.²⁴ Forty-three patients with radiological PD and a positive Octreoscan[®] (Mallinckrodt, Inc., Dublin, Republic of Ireland) or ⁶⁸Ga Dota-peptide PET completed treatment and received a cumulative activity of 18.5 or 27.8 GBq in five cycles according to baseline kidney function, reduction in bone marrow reserve, or effects of previous

therapies, all defined as risk factors. Twenty-five (58%) patients received median full dosage of 25.7 GBq (range 22.2–27.8), while the remaining 18 patients (42%) received a mean reduced dosage of 18.4 GBq (range 14.4–20.4). According to SWOG criteria, the overall response was a complete response in 7% of cases and SD in 77%, with a disease control rate (DCR) of 84%. Median response duration was 25 months (range 7–50). Median PFS was 36 months, while median OS has not yet been reached. Once again, none of the patients showed side effects after either of the Lu-PRRT dosages.

¹⁷⁷Lu-Dotatoc has been used in a number of important centers in the last few years, with a promising efficacy and toxicity profile. A recent paper by Baum et al²⁵ reported efficacy and safety data of ¹⁷⁷Lu-Dotatoc administered to 56 patients with metastatic and progressive NETs (50% GI tract, 26.8% pancreas, and 23.2% other primary sites). Median dosage was 7.0 GBq every 3 months (mean 2.1 cycles; range 1–4). Efficacy evaluation was performed using computed tomography and/or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors 1.1 criteria, and the results were stratified according to the number of administered cycles and the primary tumor origin. The overall median DCR was 93.8% for patients who received more than one cycle, while median PFS and OS were 17.4 and 34.2 months, respectively, assessed over a follow-up time (mean \pm standard deviation) of 16.1 \pm 12.4 months. Considering only the GEP-NET patients who received more than one cycle, DCR increased to 100%, while PFS was significantly higher for non-GEP-NET patients (34.5 months non-GEP-NET vs 11.9 months GEP-NET). Moreover, no serious adverse events were observed. One case of self-limiting Grade 3 myelotoxicity was reported and there were no cases of renal toxicity after treatment, even in patients with mild renal insufficiency at baseline.

PRRT retreatment in GEP-NET patients, a new therapeutic application (personal experience)

The majority of patients with GEP-NETs who relapse after therapy in the early stages of disease still have a good prognosis given the fairly indolent behavior of well-/moderately differentiated neuroendocrine tumors. At our institute, the task of choosing between the many therapeutic options available is the responsibility of a dedicated and experienced multidisciplinary team whose decision is based on the patient's medical history, current clinical conditions, and pathological stage of the disease. In this complex situation, PRRT retreatment is considered for patients who have

Table 2 Results of our experience of PRRT retreatment

Evaluation criteria	90Y-PRRT treatment	177Lu-PRRT retreatment	P-value
Number of patients	26	26	
Median activity (range)	10.8 GBq (5–14.9)	16.5 GBq (5.5–22.2)	
Median number of cycles	5 (2–7)	5 (2–5)	
CR	1	1	
PR	3	1	
SD	22	20	
PD	NA	4	
Median PFS, months (95% CI)	28 (20–36)	22 (16–nr)	0.529
Median OS, months (95% CI)		36 (4–70)	

Note: © Springer-Verlag Berlin Heidelberg 2015. Severi S, Sansovini M, Ianniello A, et al. Feasibility and utility of re-treatment with (177)Lu-DOTATATE in GEP-NENs relapsed after treatment with (90)Y-DOTATOC. *Eur J Nucl Med Mol Imaging*. 2015;42(13):1955–1963.³¹ With permission of Springer.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; nr, not reached; CI, confidence interval; PRRT, peptide receptor radionuclide therapy; NA, not applicable.

received low-dose PRRT as a first treatment and who are still in good general condition, making them amenable to further PRRT. In addition to confirmation of persistent SSTR2 receptor expression with Octreoscan or 68Ga-Dotapeptide PET, patients must have shown a good response to the first treatment (a PFS of at least 12 months is required). The few studies published on this topic are generally based on retrospective data of patients who were not homogeneously treated. In fact, reported experiences vary widely in terms of number of cycles and injected activity in both treatment and retreatment settings.^{26–30}

Our institute carried out a Phase II study³¹ to evaluate the feasibility and potential activity of retreatment with low-dosage 177Lu-Dotatate in patients previously treated with 90Y-Dotatoc. Patients were administered a dosage of 500 mCi (18.5 GBq) in five cycles performed 8 weeks apart, with the aim of not exceeding the maximum tolerable doses to the kidneys and bone marrow. The activity was selected on the basis of results from a previous Phase II trial of GEP-NET patients conducted by our team, which did not highlight a statistical difference in terms of DCR between high- and low-dosage groups. The findings prompted us to propose the low dosage for the 177Lu-Dotatate retreatment PRRT protocol.²⁴

We enrolled 26 consecutive patients previously treated with 90Y-Dotatoc and with preserved kidney and hematological parameters. Toxicity, DCR, PFS, and prognostic factors were evaluated as primary and secondary objectives. The median administered activity delivered in five cycles was 16.5 GBq. Only two cases of Grade 2 and one case of Grade 3 bone marrow toxicity were observed. One patient experienced Grade 2 renal toxicity, while another, who had previous renal problems, experienced transient Grade 3 toxicity. The DCR was 84.6% and median PFS was 22 months (95% confidence interval, 16 – not reached) compared to 28 months (95% confidence interval, 20–36) after the first 90Y-Dotatoc

treatment. The most important prognostic factors were tumor burden and the number of liver metastases (Table 2).³¹

Despite the limited number of patients involved in our study, results suggest that retreatment with low-dosage 177Lu-Dotatate can be considered as a valid therapeutic option for GEP-NET patients who relapse after previous 90Y-Dotatoc treatment (Figure 2). Obviously this kind of advanced patient represents a complex problem given the possible toxic effect of previous PRRT and concurrent therapies. Thus, all therapeutic options must be carefully examined by a multidisciplinary team of experts in the area of neuroendocrine tumors in order to offer patients the best chance of a good clinical response and longer survival.

Therapeutic strategy

In recent years, PRRT with either 177Lu-Dotatate or 90Y-Dotatoc has been shown to be highly effective and seldom toxic in progressive GI-NETs, generally obtaining results largely comparable with competitive therapies, especially in terms of PFS. Up to now, the burning issue in PRRT treatment has been whether to use 177Lu-Dotatate or 90Y-Dotatoc. We have been accustomed to evaluate differences in terms of radionuclide emission energy and peptide receptor affinity. The dosimetric implications related to lesion volume and possible kidney or bone marrow toxicity are certainly important but are not the only variables to consider.

Recent studies have shown that clinical risk factors such as hypertension, diabetes, or renal or bone marrow impairment caused by previous chemotherapy increase PRRT toxicity, and efforts have been made to identify the minimum effective activity that can make PRRT feasible for high-risk patients as well. At the same time, dosimetric studies have demonstrated that, together with the total administered activity, the total number of cycles also plays an important role in PRRT toxicity.^{17,19,32} In particular, it has been seen that a

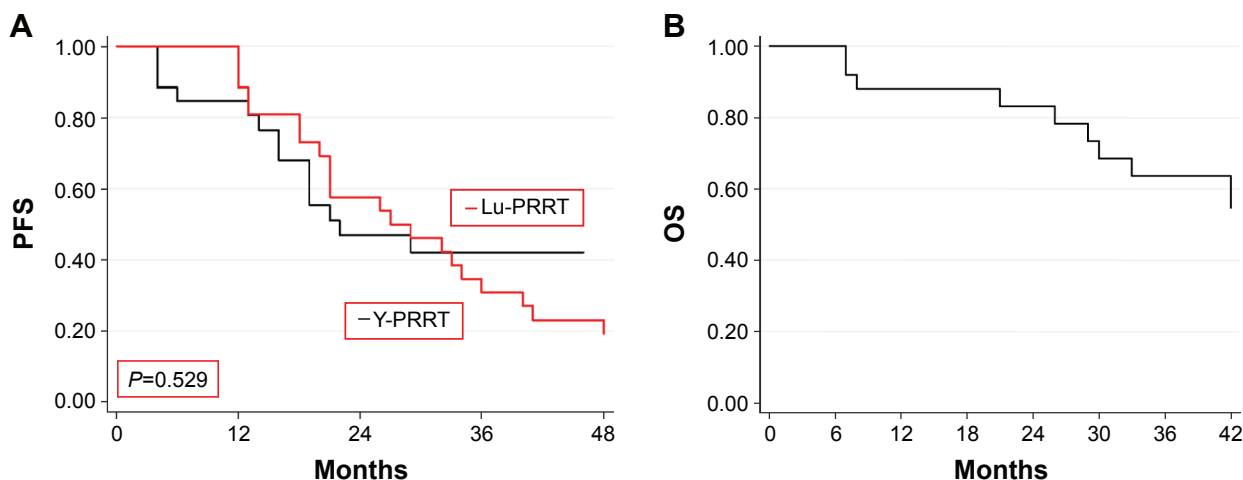


Figure 2 (A) PFS curves of the same group of patients after treatment with 90Y-Dotatoc and after retreatment with low-dose 177Lu-Dotatate. **(B)** OS curve for retreatment group.

Note: It was not possible to elaborate a posttreatment OS curve as all of the patients included in the study were originally treated in different centers in Italy.

Abbreviations: PFS, progression-free survival; OS, overall survival; 90Y-Dotatoc, 90Y-DOTA-Tyr3-octreotide; 177Lu-Dotatate, 177Lu-DOTA-Tyr3-octreotate.

higher number of cycles with the same cumulative activity protects the kidneys and bone marrow from excess radiation exposure.

There is also an evidence that higher tumor grade, FDG avidity, disease extension, and liver involvement, all considered indicators of disease aggressiveness or prognostic factors, are important aspects to be evaluated before administering PRRT. In fact, nuclear medicine physicians can improve PRRT efficacy in high-risk patients by increasing the total administered activity or the number or frequency of PRRT cycles, or by associating radiosensitizer agents such as capecitabine or capecitabine plus temozolomide, as described by the Australian group.³³ These new therapeutic options currently under consideration in several centers offer the opportunity of further customizing treatment by increasing dose intensity only when required. There is also a growing interest in studies on liquid biopsy focusing on the prognostic value of circulating agents such as RNA transcripts³⁴ or miRNA. The results of these studies will probably provide new and important parameters to increase PRRT effectiveness.

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Disclosure

The authors report no conflicts of interest in this work.

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