



Peptide Receptor Radionuclide Therapy Using ^{177}Lu -DOTATATE in Advanced Neuroendocrine Tumors (NETs) in a Limited-Resource Environment

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Abstract

Keywords

- ▶ neuroendocrine tumors (NETs)
- ▶ peptide receptor radionuclide therapy (PRRT)
- ▶ ^{177}Lu -DOTATATE
- ▶ ^{68}Ga -DOTATATE PET-CT
- ▶ $^{99\text{m}}\text{Tc}$ -octreotide scintigraphy

Background This study was conducted to evaluate the clinical efficacy and safety of peptide receptor radionuclide therapy (PRRT) using ^{177}Lu -DOTA0-Tyr3-octreotate (DOTATATE) in patients with neuroendocrine tumors (NETs).

Methods Sixteen patients with pathologically verified NETs including eight females and eight males were enrolled in this study. Before PRRT, the patients underwent ^{68}Ga -DOTATATE positron emission tomography/computed tomography or $^{99\text{m}}\text{Tc}$ -octreotide scintigraphy for evaluation of somatostatin receptor expression. Response to treatment was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). In addition, for evaluation of toxicity, monthly blood analysis was performed including hematology, renal function (creatinine) test, and liver function test. The Eastern Cooperative Oncology Group (ECOG) status

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performance was applied to estimate the patients' general condition in a scale of 0 (fully active) to 5 (dead). In addition, overall survival (OS) was calculated as the time interval from the start of PRRT to death from any reason.

Results Sixteen patients including eight females and eight males with a median age of 60.5 years (range: 24–74) were enrolled in this study. The patients underwent PRRT with a median cycle of 3.5 (range: 1–7) and a median dose of 20.35 (range: 7.4–49.95 GBq). At the end of data collection, PR, CR, SD, and PD were seen in 11, 2, 1, and 2 patients according to the RECIST, respectively. Three patients expired during or after the PRRT period. The median ECOG and Karnofsky Performance Scale was 1.5 and 75 before PRRT, which improved significantly to 1 and 80 after PRRT, respectively ($p < 0.05$). According to the Kaplan–Meier test, the median OS was 23 months (95% confidence interval: 7.90–38.09). According to the National Cancer Institute's Common Terminology Criteria for Adverse Events, three patients showed grade I and three patients showed grade II leucopenia. Furthermore, three and seven patients had grade II and grade I anemia, respectively.

Conclusion Since PRRT using ^{177}Lu -DOTATATE has a favorable response rate and few adverse effects and improves the quality of life in NETs, it can be used as an effective therapeutic option, especially in nonoperative, metastatic, and progressive NETs.

Introduction

Neuroendocrine tumors (NETs) are defined as neoplastic lesions originating from neuroendocrine cells. According to the data from the National Cancer Institute, there has been an increase in the incidence of NETs (0.3 per 100,000), which is contributed to advanced professional diagnostic tools.¹

Several treatment methods are available for treatment of NETs according to the tumor condition, including surgery as the first-line option, even in the metastasized tumors. Several palliative therapeutic options are used in nonresectable tumors, including chemotherapy and radionuclide therapy.²

A common property of NETs is overexpression of somatostatin receptors (SSTRs) leading to the establishment of alternative therapeutic option for these tumors, including radiolabeled somatostatin analogues.³

Peptide receptor radionuclide therapy (PRRT) is a very new treatment option, which includes systematic administration of radiolabeled somatostatin analogues with radiopharmaceuticals such as ^{177}Lu -DOTA0-Tyr3-octreotate (^{177}Lu -DOTATATE) to molecularly targeted malignant NETs. The results of several studies that have evaluated the clinical efficacy of PRRT with ^{177}Lu -DOTATATE in NETs have shown the long-term survival for these patients.^{1,4,5} Nevertheless, the PRRT approach is associated with few or reversible side effects in the kidney function and bone marrow, which are considered dose-limiting organs.⁶

Many studies have confirmed the promising results of ^{177}Lu -labeled PRRT for treatment of these patients through gamma- and β -emission as a theranostic agent.^{2,7,8} The purpose of this study was to evaluate the clinical efficacy and safety of PRRT with ^{177}Lu -DOTATATE in patients with NETs and the effect of this therapy on the overall survival (OS) and quality of life (QOL).

Methods

Patient Characteristics

Sixteen patients (eight males and eight females) with pathologically verified NETs were included in this study from June 2017 to April 2020. The clinical characteristic and demographic data of patients were collected. The exclusion criteria were hemoglobin less than 8.0 g/dL, serum creatinine more than 150 $\mu\text{mol/L}$ (1.7 mg/dL), creatinine clearance less than 50 mL/minute, white blood cell count less than 2,000/mm², platelet count less than 75,000/mm², and total bilirubin greater than 3 times the upper limit of normal. The study protocol was explained to patients and written consent was obtained from them. The Ethical Committee of Bushehr University of Medical Sciences approved this study (Registration code: 345).

Pretreatment Imaging

Before PRRT, the expression of SSTRs was evaluated using $^{99\text{m}}\text{Tc}$ -octreotide scintigraphy or ^{68}Ga -DOTATATE positron emission tomography/computed tomography (PET/CT). All images were reviewed by two nuclear medicine specialists. If lesions showed acceptable uptake of radiotracer (Krenning score ≥ 2) on $^{99\text{m}}\text{Tc}$ -octreotide scintigraphy and maximum standardized uptake value was higher than liver on ^{68}Ga -DOTATATE PET/CT, the patient was scheduled for PRRT with ^{177}Lu -DOTATATE.

Treatment

For PRRT, the patients were hospitalized in the dedicated theranostics center of the Department of Nuclear Medicine. The median amount of activity in each cycle was 5.5 GBq (range: 3.7–7.4). Commercial radiolabeled ^{177}Lu -DOTATATE was obtained from Pars Isotope Co., Iran.

Before administration of ^{177}Lu -DOTATATE, the probability of renal side effects was reduced by intravenous injection of

amino acid solution (2.5% arginine and 2.5% lysine, 1 L) starting 30 minutes before infusion of the radiopharmaceutical. Then, the radiopharmaceutical was injected intravenously during approximately 20 minutes.

The time interval between treatment cycles was 6 to 8 weeks. The treatment was considered unsuccessful and subsequently stopped if there were complications such as severe hematological toxicities and cardiac problems, disease progression, or death, or if the patient was unable or unwilling to continue participation.

Posttreatment Imaging

For evaluation of radiotracer distribution, scintigraphy was performed 24 and 48 hours after PRRT. Images were acquired with a dual-head gamma camera (Vertex ADAC plus) equipped with a low-energy high-resolution collimator. Energy was set at 113 KeV with an energy window of 20%. The scan was performed in whole body anterior and posterior images. In the case of borderline abnormality, single-photon emission computed tomography–SPECT–images were performed to advance the detectability of lesions. All images were reviewed by two nuclear medicine specialists.

Response Evaluation

Tumor morphology and treatment response were evaluated through follow-up imaging including CT scan and magnetic resonance imaging every 6 to 8 weeks during treatment cycles as well as 3 and 6 months after the last treatment session and assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST).⁹ According to the RECIST, response to treatment is classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Moreover, if available, some patients underwent ⁶⁸Ga-DOTATATE PET/CT for follow-up in addition to anatomical imaging.

For evaluation of safety and toxicity of PRRT, blood analysis was performed monthly after administration of ¹⁷⁷Lu-DOTATATE. Blood tests included hematology, renal function test (creatinine), and liver function test (aspartate aminotransferase and alanine aminotransferase).

PRRT-related toxicity was measured according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).

The Eastern Cooperative Oncology Group (ECOG) status performance was applied to estimate the patients' general condition in a scale of 0 (fully active) to 5 (dead). ECOG was assessed before each PRRT session and at least 3 months after the final treatment session in the follow-up visit for evaluation of any changes in the QOL.

Furthermore, OS was calculated as the time interval from the start of PRRT to death from any reason. In addition, progression-free survival (PFS) was calculated as the time from the initiation of treatment with ¹⁷⁷Lu-DOTATATE until the first evidence of progression or relapse, or to death.

Data Collection and Statistical Analysis

Disease-related data were obtained from our hospital and another clinical department. Descriptive and categorical

data are expressed as median and frequency, respectively. Chi-square test was used to analyze categorical variables. The Kaplan–Meier estimator and log-rank tests were applied to evaluate OS and the effect of multiple parameters on OS. Statistical analysis was performed using SPSS Statistics 21 (IBM Corporation, Somers, New York, United States). *p*-Values of less than 0.05 were considered significant.

Results

Patients

Sixteen NET patients including eight males and eight females were enrolled in this study. Nine cases (56%) were functional NET and seven cases (44%) were nonfunctional NET. The median age of the subjects was 60.5 years (range: 24–75). According to the medical history, three patients were hypertensive and four were diabetic. Of 16 patients, 12 were selected for PRRT according to ^{99m}Tc-octreotide scintigraphy and 4 according to ⁶⁸Ga-DOTATATE PET/CT. The primary sites of NETs were the pancreas (8/16), gastrointestinal tract (5/16), and lungs (3/16). ▶ **Table 1** summarizes the patients' characteristics. The patients presented with metastases in the liver (13/16), lymph nodes (5/16), bone (1/16), kidney (1/16), and uterus (1/16). Of 16 patients, 10, 8, and 2 patients underwent surgery, chemotherapy, and radiotherapy, respectively. The median Krenning score was 3 (range: 3–4) according to the pretreatment imaging. The patients underwent PRRT with median cycles of 3.5 (range: 1–7) and median dose of 20.35 (range: 7.4 to 49.95 GBq).

Response Rate

At the end of data collection, 11 (70%), 2 (12%), 1 (6%), and 2 (12%) patients had PR, CR, SD, and PD according to the RECIST, respectively. In addition to anatomical imaging, four patients underwent follow-up with ⁶⁸Ga-DOTATATE PET/CT, which was consistent with the results of anatomical imaging. Three patients expired during or after the PRRT period. Of nine patients with functional NET, seven cases (78%) showed a reduction in symptoms. Before PRRT, the median ECOG and Karnofsky Performance Scale (KPS) values were 1.5 and 75, which significantly improved to 1 and 80 after PRRT, respectively (*p* < 0.05). According to the Kaplan–Meier test, the median OS was 23 months (95% confidence interval: 7.90–38.09; ▶ **Fig. 1**). Furthermore, the median PFS was 12.5 months (range: 3–35).

No significant association was found between the treatment response and other variables including baseline ECOG, sex, Krenning score, tumor site, metastases, previous therapy, number of PRRT cycle, total administered dose, and PRRT-related toxicity (*p* > 0.05). ▶ **Table 2** summarizes ¹⁷⁷Lu-DOTATATE treatment profile and the treatment response in all patients.

Side Effects

In evaluation of PRRT-related toxicity according to the CTCAE, three patients showed grade I and three patients had grade II leucopenia. Furthermore, three and seven patients had grade II and grade I anemia, respectively. Serum

Table 1 Baseline characteristics and treatment outcome of all patients

Patient	Gender/Age	Sur/Rad/Ch	Primary tumor site	Metastasis	Functional	KS	HT	DM
1	F/54	+/+/+	GI	Liver, Kidney/Uterus	Yes	P	+	+
2	M/60	+/-/-	GI	Liver	Yes	3	-	-
3	F/63	+/-/+	Pancreas	Liver	No	3	-	-
4	M/68	+/-/+	Pancreas	Liver/Lymph node	No	P	-	-
5	F/27	+/-/+	Lung	Liver/Lymph node/Bone	Yes	3	-	-
6	M/69	-/-/-	GI	-	No	P	+	-
7	M/71	-/-/+	Lung	Liver	Yes	3	-	-
8	F/54	-/-/-	Pancreas	Liver	Yes	4	-	+
9	F/63	+/-/+	Lung	Liver/Lymph node/Skin	Yes	4	-	+
10	F/43	-/+/-	Pancreas	Liver	No	P	-	-
11	M/61	+/-/-	Pancreas	Liver	No	3	-	-
12	M/59	-/-/-	Pancreas	Liver/Lymph node	Yes	4	+	+
13	F/75	+/-/-	Pancreas	-	No	3	-	-
14	F/24	+/-/+	GI	Lymph node	Yes	3	-	-
15	F/62	-/-/-	GI	Liver	Yes	3	-	-
16	M/59	+/+/-	Pancreas	Liver	No	4	-	-

Abbreviations: Ch, chemotherapy; DM, diabetes mellitus; F, female; GI, gastrointestinal; HT, hypertension; KS, Krenning Score; M, male; Rad, radiotherapy; Sur, surgery.

P: The patients underwent ^{68}Ga -DOTATATE instead of $^{99\text{m}}\text{Tc}$ -octreotide scintigraphy for pretreatment evaluation of somatostatin receptor expression.

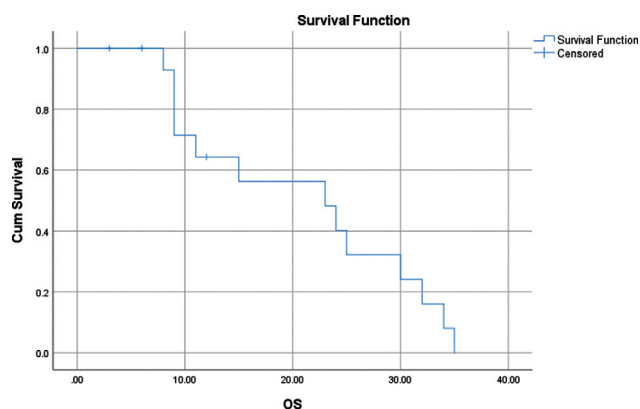


Fig. 1 Kaplan-Meier plot of overall survival (OS) of all patients. Estimated OS: 23 months (95% confidence interval: 7.90–38.09).

creatinine increased to grade I in three patients. In addition, two patients showed grade I thrombocytopenia (► **Table 3**).

► **Fig. 2** presents the outcome of PRRT in a patient with PR.

Discussion

The present study is a report of 4 years of experience with PRRT using ^{177}Lu -DOTATATE in patients with NETs. The clinical efficacy and safety of PRRT were evaluated in 16 patients with NET.

In recent decades, after it was demonstrated that NETs could be detected with radiolabeled somatostatin analogues such as ^{68}Ga -DOTATATE PET/CT and $^{99\text{m}}\text{Tc}$ -octreotide, PRRT was introduced as a therapeutic option for NETs, especially in

patients who were refractory or progressive to conventional therapeutic modalities such as surgery, somatostatin analogue therapy, and chemotherapy. Since then, several studies have evaluated the clinical efficacy and safety of PRRT.^{2,3,7,8,10–13} A phase-three trial evaluated the efficacy and safety of ^{177}Lu -DOTATATE therapy in advanced and progressive midgut NETs in comparison with somatostatin analogues therapy (control group), which resulted in an 18% response rate in the PRRT group in comparison to 3% in the control group. As for survival, 14 and 26 deaths occurred in the PRRT and control groups, respectively.¹² In another study, the efficacy of PRRT with $^{90\text{Y}}$ - or ^{177}Lu -DOTANOC as another somatostatin analogue was evaluated in patients with NET. The results showed moderate toxicity in 8/20 of the patients. In addition, of 20 patients that underwent PRRT, partial remission was seen in 5 patients, SD in 11 patients, and tumor progression in 4 patients.²

In the present study, of 16 evaluated patients, PR was found in 11 (70%), CR in 2 (12%), SD in 1 (6%), and PD in 2 (12%) patients according to the RECIST, indicating the favorable efficacy of PRRT for the treatment of patients with NET. Also, of nine patients with functional NET, seven cases (78%) showed a reduction in symptoms. In accordance with our results, Abou Jokh Casas et al reported that PRRT was effective in 69% of the patients with NETs. However, they reported progression too in 25% of the patients.⁷ Kwekkeboom et al evaluated the effectiveness of PRRT using ^{177}Lu -octreotide as a radiolabeled somatostatin analogue in patients with metastasized or inoperable endocrine gastroenteropancreatic tumors. The results showed CR in 2%, PR in

Table 2 ¹⁷⁷Lu-DOTATATE treatment profile and the treatment response in all patients

Patient	PRRT cycle	Dose (GBq)	ECOG (pre- and posttreatment)	KPS (pre- and posttreatment)	Response	CgA (pre- and posttreatment)	Toxicity	Survival (months)	PFS	Alive
1	4	29.6	1/1	80/90	PR ^a	-/9	Leucopenia (G1) Nephrotoxicity (G1) Anemia (G1)	30	30	Yes
2	5	27.75	2/1	60/80	PR	-/-	-	35	35	Yes
3	2	7.4	2/1	60/70	CR	-/-	-	34	34	Yes
4	5	37	1/0	90/100	PR	946/24	Leucopenia (G2) Anemia (G2) Nephrotoxicity (G1) Thrombocytopenia (G1)	24	24	Yes
5	6	44.4	0/0	100/100	PR ^a	73/34	Anemia (G1)	25	20	Yes
6	4	24.05	0/0	100/100	CR ^a	72/26	Leucopenia (G2)	23	23	Yes
7	1	7.4	3/3	40/40	PD	-/-	Anemia (G1)	3	3	No
8	7	49.95	0/0	100/100	PR	-/-	Leucopenia (G1) Anemia (G2)	15	15	Yes
9	2	9.25	2/2	70/70	SD	-/-	Anemia (G2) Nephrotoxicity (G1) Thrombocytopenia (G1)	6	4	No
10	3	18.5	1/1	80/80	PR ^a	-/-	Leucopenia (G2) Anemia (G1)	11	10	Yes
11	5	22.2	1/1	80/80	PR	-/-	Anemia (G1)	9	9	Yes
12	5	22.2	3/1	60/80	PR	-/-	Leucopenia (G1) Anemia (G1)	9	7	Yes
13	3	13.32	2/1	70/80	PR	-/-	Anemia (G1)	8	8	Yes
14	2	7.4	0/0	100/100	PR	-/-	-	9	9	Yes
15	3	11.1	2/1	70/90	PR	-/-	-	32	32	Yes
16	2	11.1	3/3	50/50	PD	-/-	-	12	8	No

Abbreviations: CgA, chromogranin A; CR, complete response; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Scale; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease.

^aThe patients performed follow-up ⁶⁸Ga-DOTATATE PET/CT in addition to anatomical imaging, which was in correlation with anatomical imaging.

Table 3 The ^{177}Lu -DOTATATE therapy-related toxicity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events

Side effect	Grade I	Grade II
Leucopenia	3	3
Anemia	7	3
Nephrotoxicity	2	–
Thrombocytopenia	2	–

26%, minor response in 19%, SD in 35%, and PD in 18% of 131 treated patients.³ In addition, they conducted another study to evaluate the efficacy of ^{177}Lu -octreotide in a larger group of patients with gastroenteropancreatic NETs. The results showed that of 310 treated patients, CR was observed in 2%, PR in 28%, minor response in 16%, SD in 35%, and PD in 20% of the patients.¹³ Our results were relatively in concordance with previous studies performed on resource-limited centers in India⁸ and South Africa.¹⁴ In a study performed in India by Danthala et al in evaluation of clinical efficacy of ^{177}Lu -DOTATATE in patients with NETs, it has been showed that among 40 treated patients, 10 patients (25%) had a minimal response, 13 (32.5%) had a PR, and 9 (22.5%) had SD. PD was seen in 8 patients (20%), including 6 patients who died during or after the treatment period.⁸ Vorster et al reported first results and experience with ^{177}Lu -DOTATATE in patients with NETs in South Africa. They indicated that of 48 treated patients, 22 (46%) demonstrated SD, 20 (42%) demonstrated a PR, and 6 (12%) demonstrated PD.¹⁴ It should be mentioned that these results compared favorably to chemotherapy reports in these patients. Previous studies showed PR and CR in less than 20% of the patients. In addition, PRRT showed

a better outcome compared with chemotherapy in OS, duration of response, and toxicity.^{15–17}

This study also evaluated the physical condition and QOL change of patients using KPS and ECOG scores. The results showed that KPS and ECOG improved significantly after treatment, indicating QOL improvement in the treated patients. Similarly, Khan et al evaluated the QOL of the patients with NETs that underwent PRRT using ^{177}Lu -octreotide in different aspects including KPS. They reported that the overall QOL improved significantly after PRRT. In addition, they found that KPS improved significantly in patients who responded to PRRT and worsened in patients who progressed after PRRT.¹⁸ In another study, QOL was assessed using the EORTC QLQ-C30 questionnaire—European Organization for Research and Treatment of Cancer core quality of life questionnaire-30—that was completed after each cycle of PRRT. The results showed a significant improvement in the overall QOL after PRRT. In analyzing specific aspects of the QOL, a significant improvement was found in emotional functioning, pain, and diarrhea.¹⁹

The median OS was 23 months in this study for all patients and death occurred in 18% (3/16) of the patients. In addition, the median PFS was 12.5 months (range: 3–35). There was no significant difference between OS and several baseline characteristics, which may be due to the small sample size and low number of events. Abou Jokh Casas et al reported that several factors could affect the OS after PRRT with ^{177}Lu -DOTATATE in patients with metastatic NETs including toxicity in previous treatment, tumor grade, and presence of bone lesions.⁷ Another study showed that in patients with grade 1 and 2 gastroenteropancreatic NET, PRRT resulted in a favorable response and long-term outcome, indicating that tumor grade is the most powerful predictive factor in OS.²⁰

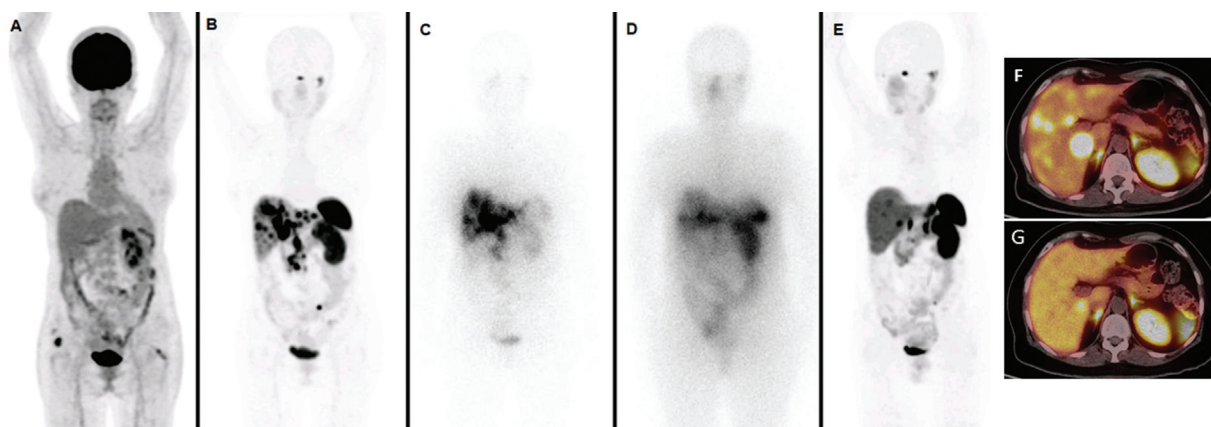


Fig. 2 A 54-year-old female with metastatic neuroendocrine tumor and refractory to chemotherapy presented for peptide receptor radionuclide therapy (PRRT). Pretreatment fluorodeoxyglucose-positron emission tomography (FDG-PET) (A) showed no radiotracer uptake (the both hot foci in the pelvis observed on FDG-PET computed tomography [CT] were due to contamination), while all lesions in the liver (maximum standardized uptake value [SUV_{max}]: 26.26, size: 34 mm), around the inferior vena cava (IVC) in the right side (SUV_{max}: 20.03; size: 23 mm), sacrum (SUV_{max}: 34.74), and also a focus in the left side of vermis on pretreatment ^{68}Ga -DOTATATE PET/CT (B) had significant somatostatin receptor expression. The patients underwent four cycles of PRRT (29.6 GBq). The posttreatment scintigraphy after first cycle (C) indicated intensive uptake of radiotracer in above-mentioned regions with significantly decrease in number and size in posttreatment scintigraphy after the fourth cycle (D). Interestingly, follow-up ^{68}Ga -DOTATATE PET-CT (E) performed 4 months after fourth cycle of PRRT showed excellent partial response with residual viable disease in the liver (SUV_{max}: 12.23; size: 20 mm), large-sized IVC metastases (SUV_{max}: 4.51; size: 16 mm), and sacrum (SUV_{max}: 7.94). In addition, the transverse view of pretherapy ^{68}Ga -DOTATATE PET-CT (F) indicates excellent response of liver lesions to PRRT compared with the transverse view of posttherapy ^{68}Ga -DOTATATE PET-CT (G).

According to the CTCAE, approximately 75% of patients developed PRRT-related toxicity in this study. The most common toxicity was anemia that occurred in 10/16 patients including grade 2 in 3 and grade 1 in 7 patients. Leucopenia developed in six including grade 2 in three and grade 1 in three patients, grade 1 nephrotoxicity in two patients, and grade 1 thrombocytopenia in two patients. A study showed hematological toxicity in 38.8% of the patients during PRRT.⁷ A multicenter study evaluated 450 patients with NETs and found that PRRT had rare serious adverse events including grade 3 leukopenia in 1.1% and grade 3 thrombocytopenia in 1.3% of the patients. Grade 4 thrombocytopenia was observed in only one patient in this study.²¹

This study had some limitations. The most important limitation was its small sample size and relatively short follow-up period. Therefore, to confirm the results, larger sample sizes and longer follow-ups are needed. Second, for more accurate decision-making, it is better to compare PRRT with other therapeutic methods such as chemotherapy and somatostatin analogues therapy, which was not possible in this study. Third, in addition to evaluation of treatment response with imaging modalities, it is better to measure chromogranin-A as a NETs marker.

Conclusion

In conclusion, since PRRT with ¹⁷⁷Lu-DOTATATE in NETs has a favorable response rate and few adverse effects and improves the QOL, it can be used as an effective therapeutic option, especially in nonoperative, metastatic, and progressive NETs.

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Conflict of Interest

None declared.

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