Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE in Advanced Neuroendocrine Tumours (NETs) in a Limited Resource Environment

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Research article

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Abstract

Background

We decided to evaluate the clinical efficacy and safety of peptide receptor radionuclide therapy (PRRT) with 177-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 for evaluation of somatostatin receptor expressing, the patients underwent 68Ga-DOTATATE PET-CT or 99mTc-octreotide scintigraphy. The treatment response was assessed according to the response evaluation criteria in solid tumors (RECIST) which was classified into 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), liver status. The Eastern Cooperative Oncology Group (ECOG) status performance was applied for estimating the patients' general condition including 0 (fully active) to 5 (dead). In addition, overall survival (OS) was calculated as the time interval between start of PRRT to death from any reason.

Results

Sixteen patients including eight females and eight males with median age of 60.5 years old with range of 24-74 were enrolled in this study. The patients underwent PRRT with median cycles of 3.5 with range of 1-7 and median dose of 20.35 with range of 7.4 to 49.95 GBq. At the end of data collection, 11/16 patients had PR, 2/16 showed CR, 1/16 showed SD and 2/16 showed PD according to the RECIST. 3 patients were expired during and after the PRRT period time. Before PRRT, the medians of ECOG and KPS were 1.5 and 75 which after treatment were, significantly, improved to 1 and 80, respectively ($p<0.05$). According to the Kaplan-Meier test, the median of OS was obtained 23 months (95%CI:7.90-38.09). According to the CTCAE, 3 patients showed grade I and 3 other showed grade II leucopenia. Furthermore, 3 and 7 patients had grade II and grade I anemia, respectively.

Conclusion

It can be concluded that, since PRRT with 177Lu-DOTATATE in NETs has favorable response rate, few adverse effects and leads to improvement in QOL, it can be used as an effective therapeutic option specially in nonoperative, metastatic and progressive NETs.

Introduction

Neuroendocrine tumors (NETs) defined as neoplasms originated from cells of the nervous systems and endocrine (hormonal). According to the data from the National Cancer Institute, it has been seen an increased incidence rates of (NETs) (0.3 per 100000) that is contributed with progressed professional diagnostic tools[1].

For treatment of NETs, based on tumor condition, several treatment methods are available which the surgery is first line, even in the metastasized tumors. In the nonresectable tumors, several palliative therapeutic options have been used including chemotherapy and radionuclide therapy[2].

An exclusive properties of NETs is overexpression of somatostatin receptors (SSTRs) leading to establishment of alternative therapeutic option for these tumors including radiolabeled somatostatin analogues[3].

Nowadays, peptide receptor radionuclide therapy (PRRT) is developed as systematic administration of radiolabeled somatostatin analogues with radiopharmaceuticals such as 177Lu- DOTA0-Tyr3-octreotate (177Lu-DOTATATE) to molecularly targeted malignant NETs. There are several studies about the clinical efficacy of PRRT with 177Lu-DOTATATE in NETs demonstrated the long-term survival for these patients [1, 4, 5]. Nevertheless, the PRRT approach has demonstrated low or reversible side effects on kidneys function and bone marrow that introduced as dose-limiting organs [6].

Many studies have confirmed promising results of 177Lu-labeled PRRT for treatment of these patients through gamma and beta emission as theranostic agent [2, 7, 8]. The purpose of this study is to evaluate the clinical efficacy and safety of PRRT with 177Lu-DOTATATE in patients with NETs and impact of this therapy on overall survival 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. All clinical characteristic and demographic information of patients were documented. Exclusion criteria included hemoglobin level < 8.0 g/deciliter; serum creatinine range > 150 µmol /liter (1.7 mg per deciliter), a creatinine clearance of < 50 ml/minute, a white blood cell count < 2000/millimeter^2; a platelet count of < 75,000 / millimeter^2; a total bilirubin level > 3 times the upper limit of the normal range; a serum albumin level of > 3.0 g/deciliter.

Pre-treatment Imaging

Before PRRT, the expression of somatostatin receptors was evaluated through 99mTc-octerotide scintigraphy or 68Ga-DOTATATE PET/CT. All images were reviewed by two nuclear medicine specialists. If lesions showed acceptable uptake of radiotracer (Krenning score ≥ 2) on 99mTc-octerotide scintigraphy and SUVmax more than liver on 68Ga-DOTATATE PET/CT, the patient was candidate for PRRT with 177Lu-DOTATATE.

Treatment

For PRRT, the patients were hospitalized in the dedicated theranostics center of Department of Nuclear Medicine. In each PRRT cycle, the patients received 3.7 to 7.4 GBq of 177Lu-DOTATATE. Commercial radiolabeled 177Lu-DOTATATE was obtained from Pars isotope co., Iran.

Before administration of 177Lu-DOTATATE, renal side effect was decreased through intravenously injection of amino acid solution (2.5% arginine and 2.5% lysine, 1 L) which was started 30 minutes before infusion of the radiopharmaceutical. After that, the radiopharmaceutical was injected intravenously during about 20 minutes.

The time interval between treatment cycles were 6-8 week. The treatment was considered unsuccessful and subsequently stopped if there were complications, disease progression, inability or unwilling of patient to participate and death.

Post-treatment Imaging

For evaluation of radiotracer distribution, scintigraphy was performed at 24 and 48 hours after PRRT. Images were acquired with a dual-head gamma camera (Vertex ADAC plus) equipped with low energy high resolution collimator and the energy was set on 113 KeV with energy window of 20%. The scan was performed in whole body and SPECT if needed.

Response Evaluation

The tumor morphological assessment and treatment response evaluated through follow-up imaging including CT scan, MRI every 6-8 weeks during treatment cycles as well as 3 and 6 months after the lost treatment session and assessed according to the response evaluation criteria in solid tumors (RECIST)[9]. According to RECIST, the treatment response was classified into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Also, if available, some patients performed 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 haematology, renal function (creatinine), liver status (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).

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

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

In addition, overall survival (OS) was calculated as the time interval between start of PRRT to death from any reason.

Data collection and Statistical Analysis

The disease-related data were obtained from our hospital and another clinical department. The descriptive and categorial data were expressed as median and frequency, respectively. For analyzing of categorial variables, Chi-square test was used. For evaluating OS and the impact of multiple parameters on OS, the Kaplan-Meier estimator and log-rank tests were used. Statistical analysis was performed using SPSS Statistics 21 (IBM Corporation, Somers, NY, USA). P-value of less than 0.05 was considered statistically significant.

Results

Patients

16 NET patients included 8 males and 8 females were enrolled in this study. The median age was 60.5 years old (range: 24-75). According to the medical history, 3 patients were hypertensive and 4 were diabetic. Of 16 patients, 12 patients were selected for PRRT according to the 99mTc-octerotide scintigraphy and 4 according to the 68Ga-DOTATATE PET/CT. The primary sites of NETs were in the pancreas (8/16), gastrointestinal (GI) (8/16), and lung (3/16). Table 1 summarizes patient characterization. The patients presented with metastases in Liver (13/16), lymph node (LN) (5/16), bone (1/16), kidney (1/16) and uterus (1/16). Of 16 patients, 10, 8 and 2 patients were performed surgery, chemotherapy and radiotherapy, respectively. The median of krenning score was obtained 3 with range of (3-4) according to the pre-treatment imaging. The patients underwent PRRT with median cycles of 3.5 with range of 1-7 and median dose of 20.35 with range of 7.4 to 49.95 GBq.

Response Rate

At the end of data collection, 11/16 patients had PR, 2/16 showed CR, 1/16 showed SD and 2/16 showed PD according to the RECIST. In addition to anatomical imaging, 4 patients performed follow-up 68Ga-DOTATATE PET/CT which was in correlation with results of anatomical imaging. 3 patients were expired during and after the PRRT period time. Before PRRT, the medians of ECOG and KPS were 1.5 and 75 which after treatment were, significantly, improved to 1 and 80, respectively ($p<0.05$). according to the Kaplan-Meier test, the median of OS was estimated 23 months (95%CI:7.90-38.09) (figure 1). We found no significant difference concerning OS in comparison with other factors including baseline ECOG, sex, krenning score, tumour site, metastases, previous therapy, number of PRRT cycle, total administered dose and PRRT related toxicity ($p<0.05$).

Side Effects

In evaluation of PRRT related toxicity according to the CTCAE, 3 patients showed grade I and 3 other showed grade II leucopenia. Furthermore, 3 and 7 patients had grade II and grade I anemia, respectively. Serum creatinine in 3 patients increased to grade I. In addition, 2 patients showed grade I thrombocytopenia (Table 2).

Figure 2 presents the outcome of PRRT in a patient with PR.

Discussion

In this study, we reported our 4 years' experience in PRRT with 177Lu-DOTATATE in patients with NETs. We evaluated the clinical efficacy and safety of PRRT in 16 patients with NET.

In the recent decades, after it has been demonstrated that NETs can be detected with radiolabeled somatostatin analogues such as 68Ga-DOTATATE PET/CT and 99mTc-octreotide, PRRT has been introduced as a therapeutic option for NETs, especially in patients who were refractory or progressive to conventional therapeutic modalities such as surgery, somatostatin analogues therapy and chemotherapy. From time of introducing, several studies have been performed for evaluation of clinical efficacy and safety of PRRT [2, 3, 7, 8, 10-13]. In a phase 3 trial, efficacy and safety of 177Lu-DOTATATE therapy in advanced and progressive midgut NETs in comparison with somatostatin analogues therapy (control group) had been evaluated which resulted in 18% response rate in PRRT group in comparison with 3% in the control group. In the evaluation of survival, 14 and 26 death occurred in the PRRT and control group, respectively. [12]. In another study, efficacy of PRRT with 90Y- or 177Lu-DOTANOC as another somatostatin analogue had been evaluated in patients with NET which revealed moderate toxicity in 8/20 patients. In addition, of 20 patients underwent PRRT, a partial remission was found in 5 patients, stable disease in 11 patients, and tumor progression in 4 patients [2].

In our study, according to RECIST, of 20 evaluated patients, PR was found in 11, CR in 2, SD in 1 and PD in 2 patients which demonstrated favorable efficacy of PRRT in treatment of patients with NET. In concordance to our results, E. Abou Jokh Casas et al reported effectiveness of PRRT in 69% of patients with NETs. However, they reported progression in 25% of patients [7]. Dik J. Kwekkeboom et al evaluated effectiveness of PRRT with 177Lu-octreotide as a radiolabeled somatostatin analogue in patients with metastasized or inoperable endocrine gastroenteropancreatic tumors that resulted in among 131 treated patients, CR in 2%, PR in 26%, minor response in 19%, SD in 35% and PD in 18% of patients [3]. Also, in another study, they evaluated efficacy of 177Lu-octreotide in larger group of patients with gastroenteropancreatic neuroendocrine tumors. They reported 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 patients [13]. It should be mentioned that these results compare favorably to chemotherapy reports in these patients. Previous studies showed PR and CR in less than 20% of patients. In addition, PRRT showed better outcome than chemotherapy in OS, duration of the response and toxicity [14-16].

In this study, we evaluated physical condition and change in QOL of patients with assessment of KPS and ECOG scores. Our results indicated that after treatment, KPS and ECOG were significantly improved compared to before treatment which revealed improvement in QOL of treated patients. In concordance with our results, Saima Khan et al evaluated QOL of patients with NETs underwent PRRT with 177Lu-octreotide in different aspects including KPS. They reported that after PRRT overall QOL significantly improved. In addition, in evaluation of KPS, they indicated that KPS significantly improved in patients responded to PRRT and deteriorated in patients progressed after PRRT [17]. In another study, QOL was assessed with EORTC QLQ-C30 questionary completed after each cycle of PRRT indicated overall QOL was significantly improved after PRRT. In analyzing specific aspects of QOL, they reported significant improvement in emotional functioning, pain and diarrhea [18].

The median OS in this study was 23 months for all patients and death occurred in 18% (3/16) of patients. There was no significant difference concerning OS compared to several baseline characteristics of patients which may be due to the small sample size and low number of events. Abou Jokh Casas E et al reported that several factors can affect the OS after PRRT with 177Lu-DOTATATE in patients with metastatic NETs including toxicity in previous treatment, tumor grade and presence of bon lesions [7]. In another study, it has been shown that in patients with grade 1 and 2 gastroenteropancreatic NET, PRRT resulted favorable response and long term outcome indicated that tumor grade is the most powerful predictive factor in OS [19].

According to the CTCAE, in this study, approximately 75% of patients developed PRRT related toxicity. Most common toxicity was anemia which occurred in 10/16 patients including grade 2 in 3 and grade 1 in 7 patients. Leucopenia developed in 6 including grade 2 in 3 and grade 1 in 3 patients, nephrotoxicity of grade 1 in 2 and thrombocytopenia of grade 1 in 2 of patients. In a study, it has been reported that during PRRT, hematological toxicity had been observed in 38.8% of patients [7]. A multicenter study evaluated 450 patients with NETs, it has been revealed that PRRT has rare serious adverse events including leukopenia of grade 3 in 1.1% and thrombocytopenia of grade 3 in 1.3%, and grade 4 thrombocytopenia was observed in only one patient [20].

This study has some limitations. First, the major limitation is small sample size and relatively short follow-up period time that for confirmation of results, very larger number of patients and longer follow-up time is needed. Second, for more accurate decision, it was better to compare PRRT with other therapeutic methods such as chemotherapy and somatostatin analogues therapy, but it was not possible in this study. Third, beside to evaluation of treatment response with imaging modalities, it was better measure chromogranin A (CgA) as a NETs marker.

Conclusion

It can be concluded that, since PRRT with 177Lu-DOTATATE in NETs has favorable response rate, few adverse effects and leads to improvement in QOL, it can be used as an effective therapeutic option specially in nonoperative, metastatic and progressive NETs.

Abbreviations

NET: neuroendocrine tumor; PRRT: peptide receptor radionuclide therapy; RECIST: response evaluation criteria in solid tumors; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease; ECOG: Eastern Cooperative Oncology Group; OS: overall survival; QOL: quality of life; DOTATATE: DOTA0-Tyr3-octreotate; KS: Krenning score; GI: gastrointestinal; LN: lymph node; GBq: gigabecquerel; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Declarations

Authors' contributions

MZ, INP, MRR, SJR: study design and data collection, SHZ: writing and data collection, EJ: writing, data collection and statistical analysis, ALA: data collection, HD: data collection, MMP: data collection, NJ: writing, MA: writing, statistical analysis, study design and data collection. All authors read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

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.

Consent for publication

Not Applicable.

Competing interests

The authors declare no conflicts of interest.

References

1. Yao, J.C., et al., *One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States.* Journal of clinical oncology, 2008. **26**(18): p. 3063-3072.
2. Frilling, A., et al., *Treatment with 90Y-and 177Lu-DOTATOC in patients with metastatic neuroendocrine tumors.* Surgery, 2006. **140**(6): p. 968-977.
3. Kwekkeboom, D.J., et al., *Radiolabeled somatostatin analog [177Lu-DOTA0, Tyr3] octreotate in patients with endocrine gastroenteropancreatic tumors.* Journal of Clinical Oncology, 2005. **23**(12): p. 2754-2762.
4. Kwekkeboom, D.J., et al., *Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors.* Endocrine-related cancer, 2010. **17**(1): p. R53-R73.
5. Gabriel, M., et al., *Twelve-year follow-up after peptide receptor radionuclide therapy.* Journal of Nuclear Medicine, 2019. **60**(4): p. 524-529.
6. Bodei, L., et al. *Radiolabeled somatostatin analogue therapy of gastroenteropancreatic cancer.* in *Seminars in nuclear medicine*. 2016. Elsevier.
7. Casas, E.A.J., et al., *Evaluation of 177Lu-Dotatate treatment in patients with metastatic neuroendocrine tumors and prognostic factors.* World Journal of Gastroenterology, 2020. **26**(13): p. 1513.
8. Danthala, M., et al., *177 Lu-DOTATATE therapy in patients with neuroendocrine tumours: 5 years' experience from a tertiary cancer care centre in India.* European journal of nuclear medicine and molecular imaging, 2014. **41**(7): p. 1319-1326.
9. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* European journal of cancer, 2009. **45**(2): p. 228-247.
10. Bodei, L., et al., *Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90 Y-DOTATOC and 177 Lu-DOTATATE: the role of associated risk factors.* European journal of nuclear medicine and molecular imaging, 2008. **35**(10): p. 1847-1856.
11. Forrer, F., et al., *Treatment with 177Lu-DOTATOC of patients with relapse of neuroendocrine tumors after treatment with 90Y-DOTATOC.* Journal of Nuclear Medicine, 2005. **46**(8): p. 1310-1316.
12. Strosberg, J., et al., *Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors.* New England Journal of Medicine, 2017. **376**(2): p. 125-135.
13. Kwekkeboom, D.J., et al., *Treatment with the radiolabeled somatostatin analog [177Lu-DOTA0, Tyr3] octreotate: toxicity, efficacy, and survival.* Journal of Clinical Oncology, 2008. **26**(13): p. 2124-2130.

14. Bajetta, E., et al., *Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours?* Cancer chemotherapy and pharmacology, 2007. **59**(5): p. 637-642.
15. Ducreux, M.P., et al., *A phase II study of irinotecan with 5-fluorouracil and leucovorin in patients with pretreated gastroenteropancreatic well-differentiated endocrine carcinomas.* Oncology, 2006. **70**(2): p. 134-140.
16. Ansell, S.M., et al., *A Phase II study of high-dose paclitaxel in patients with advanced neuroendocrine tumors.* Cancer: Interdisciplinary International Journal of the American Cancer Society, 2001. **91**(8): p. 1543-1548.
17. Khan, S., et al., *Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0, Tyr3] octreotate.* Journal of nuclear medicine, 2011. **52**(9): p. 1361-1368.
18. Marinova, M., et al., *Quality of life in patients with midgut NET following peptide receptor radionuclide therapy.* European journal of nuclear medicine and molecular imaging, 2019. **46**(11): p. 2252-2259.
19. Ezziddin, S., et al., *Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-octreotate.* Journal of nuclear medicine, 2014. **55**(2): p. 183-190.
20. Hörsch, D., et al., *Effectiveness and side-effects of peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow-up.* European Journal of Cancer, 2016. **58**: p. 41-51.

Tables

Table 1. Baseline characteristics and treatment outcome of all patients. F:female, M:male, KS: Krenning Score, GI: gastrointestinal, Sur: surgery, Rad: radiotherapy, Ch: chemotherapy, HT: hypertension, DM: diabetes mellitus, CgA: Chromogranin A, PRRT: peptide receptor radionuclide therapy, ECOG: Eastern Cooperative Oncology Group, KPS: Karnofsky Performance Scale, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Patient	Gender/Age	Sur/Rad/Ch	Primary tumor site	Metastasis	KS	HT	DM	PRRT cycle	Dose (GBq)	ECOG (pre- and post-treatment)	KPS (pre- and post-treatment)	Response	CgA (pr and pos treatme
1	F/54	+/+/+	GI	Liver, Kidney/ Uterous	P	+	+	4	29.6	1/1	80/90	PR*	-/9
2	M/60	+/-/-	GI	Liver	3	-	-	5	27.75	2/1	60/80	PR	-/-
3	F/63	+/-/+	Pancreas	Liver	3	-	-	2	7.4	2/1	60/70	CR	-/-
4	M/68	+/-/+	Pancreas	Liver/ Lymph node	P	-	-	5	37	1/0	90/100	PR	946/24
5	F/27	+/-/+	Lung	Liver/Lymph node/ Bone	3	-	-	6	44.4	0/0	100/100	PR*	73/34
6	M/69	-/-/-	GI	-	P	+	-	4	24.05	0/0	100/100	CR*	72/26
7	M/71	-/-/+	Lung	Liver	3	-	-	1	7.4	3/3	40/40	PD	-/-
8	F/54	-/-/-	Pancreas	Liver	4	-	+	7	49.95	0/0	100/100	PR	-/-
9	F/63	+/-/+	Lung	Liver/ Lymph node/ Skin	4	-	+	2	9.25	2/2	70/70	SD	-/-
10	F/43	-/+/-	Pancreas	Liver	P	-	-	3	18.5	1/1	80/80	PR*	-/-
11	M/61	+/-/-	Pancreas	Liver	3	-	-	5	22.2	1/1	80/80	PR	-/-
12	M/59	-/-/-	Pancreas	Liver/ Lymph node	4	+	+	5	22.2	3/1	60/80	PR	-/-
13	F/75	+/-/-	Pancreas	-	3	-	-	3	13.32	2/1	70/80	PR	-/-
14	F/24	+/-/+	GI	Lymph node	3	-	-	2	7.4	0/0	100/100	PR	-/-
15	F/62	-/-/-	GI	Liver	3	-	-	3	11.1	2/1	70/90	PR	-/-
16	M/59	+/+/-	Pancreas	Liver	4	-	-	2	11.1	3/3	50/50	PD	-/-

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

P: The patients were underwent 68Ga-DOTATATE instead of 99mTc-octreotide scintigraphy for pre-treatment evaluation of SSTR expression.

Table 2. The 177Lu-DOTATATE therapy related toxicity according to the CTCAE

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

Figures

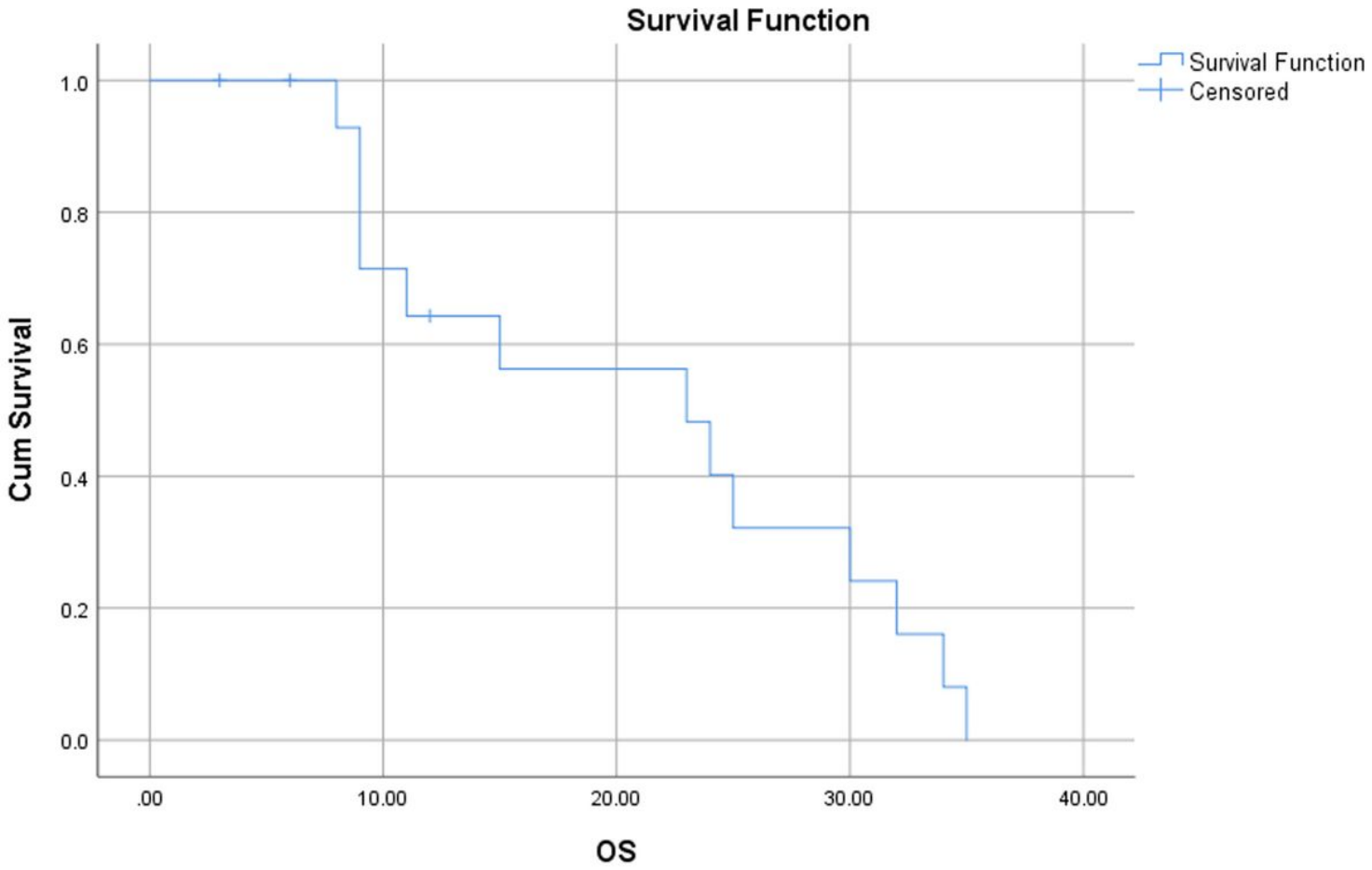

Figure 1

Kaplan-Meier plot of overall survival (OS) of all patients. Estimated OS: 23 months (95%CI:7.90-38.09).

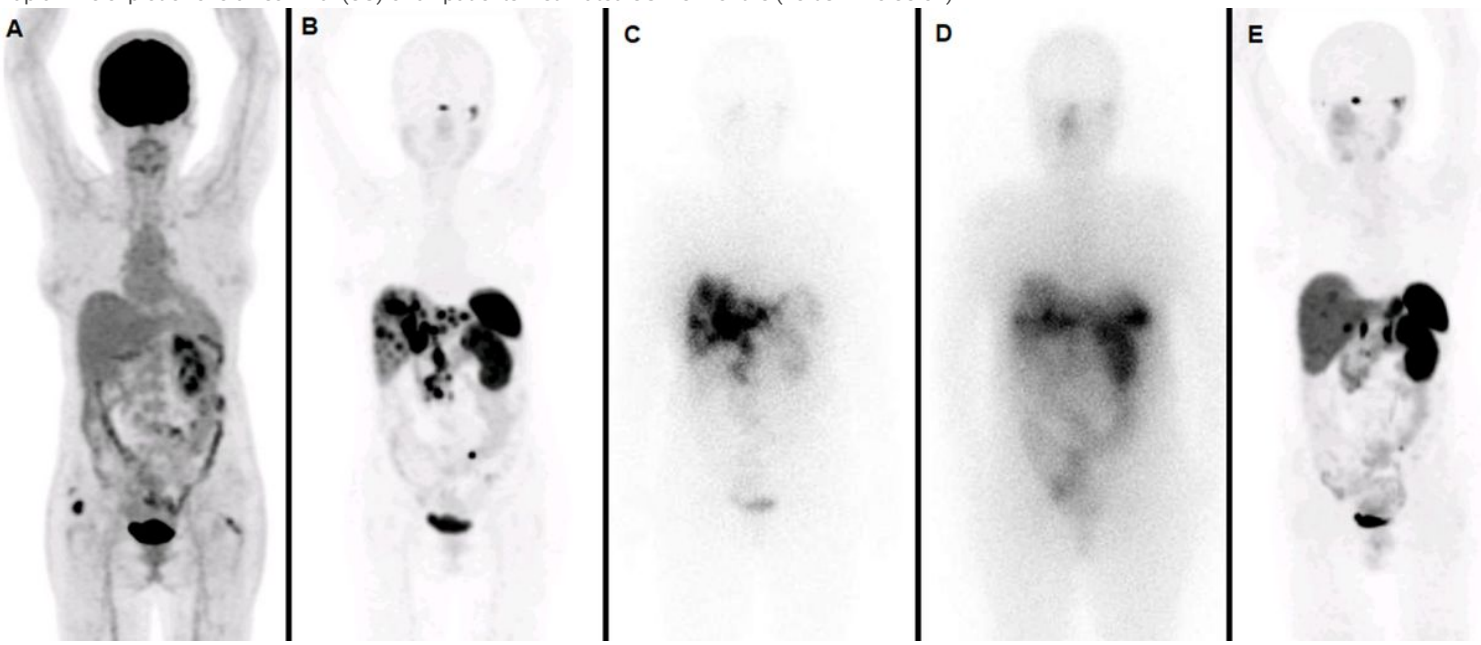

Figure 2

A 54-year-old female with metastatic neuroendocrine tumors and refractory to chemotherapy presented for PRRT. Pre-treatment FDG PET (A) showed no radiotracer uptake (the both hot foci in the pelvis observed on FDG PET-CT were due to contamination), while all lesions in the liver (SUV max:26.26, size: 34 mm), around the IVC in the right side (SUV max: 20.03; size: 23 mm), sacr-um (SUV max: 34.74) and also a focus in the left side of vermis on pretreatment

68Ga-DOTATATE PET/CT (B) had significant SSTR expression. The patients underwent 4 cycles of PRRT (29.6 GBq). The post-treatment scintigraphy after 1st cycle (C) indicated intensive uptake of radiotracer in above mentioned regions with significantly decreased in number and size in post-treatment scintigraphy after 4th cycle (D). Interestingly, follow-up 68Ga-DOTATATE PET-CT (E) preformed 4 months after 4th 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).