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ORIGINAL ARTICLE

Extended peptide receptor radionuclide therapy: evaluating nephrotoxicity and therapeutic effectiveness in neuroendocrine tumor patients receiving more than four treatment cycles

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Abstract

Purpose Currently, the most used peptide receptor radionuclide therapy (PRRT) regimen for neuroendocrine tumors comprises 4 treatment cycles, and there is not enough large-scale data to support the safety of more individualized extended PRRT. This study aims to evaluate the therapeutic effectiveness and potential nephrotoxicity related to PRRT using more than four treatment cycles.

Methods In this retrospective analysis, we included patients who had received at least four PRRT cycles and had available follow-up data. We analyzed renal function indicators before and after multiple treatments, comparing nephrotoxicity in patients receiving four cycles ("standard") with those receiving more than four ("extended treatment"). Nephrotoxicity was assessed via creatinine levels and CTCAE creatinine grades. Treatment effectiveness was gauged using Kaplan–Meier survival analysis, focusing on overall survival and disease-specific survival (DSS). Statistical analyses were performed using SPSS version 26 (IBM), R 4.2.3, and GraphPad Prism 9.0.0. Statistical significance was defined as a *P*-value of less than 0.05.

Results Our study cohort consisted of 281 patients in the standard group and 356 in the extended treatment group. No significant differences in baseline characteristics or renal function were noted between the two groups pre-treatment. Mean post-treatment creatinine levels did not significantly differ between the standard (89.30 ± 51.19 µmol/L) and extended treatment groups (93.20 ± 55.98 µmol/L; $P = 0.364$). Similarly, there was no statistical significance between the CTCAE creatinine grades of the two groups ($P = 0.448$). Adverse renal events were observed in 0.4% of patients in the standard group and 1.1% in the extended treatment group. After a median follow-up time of 88.3 months, we found that median overall survival was significantly higher in the extended treatment group (72.8 months) compared to the standard treatment group (52.8 months). A Cox regression analysis further supported these findings, indicating a better prognosis for the extended treatment group in terms of overall survival (HR: 0.580, $P < 0.001$) and DSS (HR: 0.599, $P < 0.001$).

Conclusion Our findings suggest that extending PRRT treatment beyond the standard four cycles may be a safe and effective therapeutic strategy for NET patients. This approach could be particularly beneficial for patients experiencing disease recurrence or progression following standard treatment.

Keywords Neuroendocrine tumors (NETs) · Nephrotoxicity · Peptide receptor radionuclide therapy (PRRT) · Prognosis

Introduction

Neuroendocrine tumors (NETs) comprise a heterogeneous group of malignancies originating from diffuse neuroendocrine cells. While surgical resection is often the primary treatment modality, its feasibility is limited in cases of widespread tumor proliferation or when crucial tissues and vessels are jeopardized. In such instances, Peptide Receptor Radionuclide Therapy (PRRT) has emerged as a significant therapeutic alternative [1].

PRRT typically entails four standard treatment cycles; four is the number of cycles that, according to initial research, gives an acceptable balance of treatment efficacy and renal toxicity, as irradiation of renal glomeruli and tubules are caused during proximal tubular reabsorption of radioligands [2–4], and PRRT extended beyond four cycles

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is associated with concerns about renal toxicity from a higher cumulative dosage [5, 6]. A contentious point in the field is whether there is a cumulative dosage beyond which renal failure risk becomes significant. In addition to limiting the number of cycles given, protective efforts include co-infusion of amino acids for competitive inhibition [3, 7].

Due to the individualistic nature of patient needs, this four-cycle regimen may not be optimal for all patients [8]. Notably, a subset of patients displays suboptimal disease control or progression after four PRRT cycles [9, 10]. Comprehensive, large-scale studies on this are currently limited, although several small-scale studies have highlighted the safety and efficacy of salvage retreatment [11, 12].

With the aim of exploring the outcomes of NET patients treated with four or more cycles of PRRT, this study investigates renal toxicity and treatment effectiveness. The insights we offer are reinforced by robust, long-term follow-up data, potentially contributing valuable knowledge to this area of inquiry.

Materials and methods

Study population

Our study strictly adhered to all legal requirements, including ethical guidelines and local radiation protection standards, throughout its duration. Conforming to the regulations set forth by the German Federal Office for Radiation Protection pertaining to radiation safety, our study received approval from the local ethics committee at Zentralklinik Bad Berka. The study population consisted of adult patients with progressive histopathologically confirmed neuroendocrine neoplasms (NENs), primarily demonstrating high SSTR expression, who had exhausted all standard treatment options. We included patients who had undergone 4 or more treatment cycles of PRRT and had post-treatment follow-up information and excluded patients who underwent peptide receptor chemo-radionuclide therapy (PRCRT), either during PRRT or upon restaging, excluding TACE. Prior to initiating therapy, we obtained written informed consent from each participant. We calculated the age of patients to the date of their initial PRRT treatment.

Radiopharmaceuticals' preparation and treatment protocol

Radiopharmaceuticals for imaging and therapy, including ^{68}Ga, ^{177}Lu and ^{90}Y labeled DOTATOC, DOTATATE, and DOTANOC, were synthesized in strict accordance with our institution's GMP protocol [13]. The radionuclide ^{68}Ga was obtained in-house from a ^{68}Ge/^{68}Ga generator. The labeling of DOTA-conjugated peptides with ^{177}Lu and ^{90}Y was performed as previously published [14]. High-performance liquid chromatography (HPLC) was used for quality control. The radiochemical purity was always greater than 99%. During the PRRT, every patient was co-infused with 1600–2000 mL of a reno-protective amino acid mixture of 5% Lysine·HCl and 10% L-Arginine·HCl in 250 mL NaCl at pH 7.4 and osmolarity of 400 moSm/L for renal protection. Starting in January 2007, patients treated with ^{90}Y/^{177}Lu DOTATATE were additionally co-infused with succinylated gelatin.

Patients were given different radionuclide treatment options, including [^{177}Lu]Lu-PRRT, [^{90}Y]Y-PRRT, DUO-PRRT (individualized and sequential ^{90}Y- and ^{177}Lu-PRRT), and TANDEM-PRRT (simultaneous application of ^{90}Y- and ^{177}Lu-PRRT). The treatment dosage was personalized, guided by the Bad Berka Score (BBS) [15], which considers factors such as tumor uptake seen in [^{68}Ga]Ga-SSTR PET/CT scans, renal function, hematological reserves, liver and extra-hepatic tumor involvement, Ki-67 index, [^{18}F]F-FDG PET/CT status, and general patient health (Karnofsky Performance Scale). The decision to use ^{90}Y and/or ^{177}Lu was influenced by tumor size, renal and hematological health, past treatments, and other factors outlined by the BBS.

Renal function assessment and follow-up

All relevant data were systematically recorded in a structured database (encompassing over 250 individual data points per patient). Before each PRRT cycle and during follow-ups, renal function parameters, such as serum creatinine, blood urea nitrogen, cGFR, and electrolytes, were assessed. Patients were re-evaluated biannually until deceased. Treatment-induced adverse events were categorized following the Common Terminology Criteria for Adverse Events (CTCAE v.5.0). Restaging was performed with SSTR PET/CT every 3–4 months after PRRT. The follow-up time was calculated from the time of the first treatment until death or February 2018. The patient's death data, including the cause of death, were recorded, and the disease-specific mortality was analyzed according to whether or not the patient died due to tumor progression.

Statistical analysis

Quantitative data were denoted as mean ± SD. The frequency data of baseline characteristics were compared using the chi-square test or Fisher's exact test. The creatinine values between the standard treatment and the extended treatment groups were compared using an unpaired *t*-test. The correlation between the times of treatment and creatinine value after treatment was analyzed by Spearman's correlation coefficient. Survival curves for OS (Overall Survival) and DSS (Disease-Specific Survival) were estimated by

Kaplan–Meier analysis, and significance was tested by the log-rank test. Univariate analysis and multivariate analysis were performed by the Cox Proportional Hazards Model to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for potential prognostic factors. The statistical analysis was 2-tailed and conducted by SPSS version 26 (IBM), R 4.2.3, and GraphPad Prism 9.0.0. A P value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

In this study, we included a total of 637 patients who underwent at least 4 treatment cycles, of which 281 received the standard 4 treatment cycles, and 356 received more than 4 treatments. All patients had confirmed tracer uptake on pretreatment SSTR-targeted PET/CT. 183 patients had received ^{177}Lu, 38 patients had received ^{90}Y, and 416 patients had received combination therapy. There was no statistically significant difference between the two groups in terms of age, sex distribution, primary tumor site, quantitative creatinine level, and grading before treatment (Table 1).

Table 1 Baseline information of both treatment groups

	Standard ($n=281$)	Extended ($n=356$)	P
Age	59.39 ± 11.54	59.48 ± 10.00	0.916
Gender			0.949
Male	157 (55.9)	198 (55.6)	
Female	124 (44.1)	158 (44.4)	
Primary site			0.654
Midgut	84 (29.9)	105 (29.5)	
Pancreas	102 (36.3)	133 (37.4)	
Stomach	2 (0.7)	5 (1.4)	
Cup	38 (13.5)	44 (12.4)	
Thymus/Mediastinum	3 (1.1)	2 (0.6)	
Lung	16 (5.7)	32 (9.0)	
Colon	1 (0.4)	1 (0.3)	
Rectum	12 (4.3)	16 (4.5)	
Others	23 (8.2)	18 (5.1)	
Baseline Creatinine	77.48 ± 20.19	76.78 ± 17.96	0.644
Creatinine grading			0.121
G0	229 (81.5)	300 (84.3)	
G1	49 (17.4)	56 (15.7)	
G2	3 (1.1)	0	
Radionuclides			< 0.001
^{177}Lu	113 (40.2)	70 (19.7)	
^{90}Y	21 (7.5)	17 (4.8)	
^{177}Lu + ^{90}Y	147 (52.3)	269 (75.6)	

Renal function assessment

Comparing the follow-up results of the two groups, there was no significant difference in the composition of creatinine grades after treatment, $P=0.448$ (Fig. 1 and Table 2), or in mean creatinine, $P=0.364$ (Table 2).

Correlation between more treatment cycles and renal function

There were 3260 treatment cycles in the total population of 637 patients, 1124 cycles in the standard treatment group, and 2136 cycles in the more than 4 cycles group. The average cumulative dose in the standard treatment dose group was 22.67 ± 5.39 GBq (range, 6.5–35.6 GBq), and in the extended treatment group 32.10 ± 9.28 GBq (range, 9.0–65.9 GBq). The results of the correlation analysis between creatinine levels and the number of treatment cycles showed no statistically significant correlation ($r=0.064$, $P=0.105$) (Fig. 2, Table 3), and the total cumulative treatment dose ($r=-0.008$, $P=0.834$), ^{90}Y treatment dose ($r=0.057$. $P=0.153$), and ^{177}Lu treatment dose ($r=-0.030$, $P=0.444$) also showed no statistical significance.

Then, we divided the patients into 3 groups according to the number of treatments and analyzed the effect of cumulative dose on renal function in patients who received more than 6 treatments. The results showed that there was no statistically significant difference in creatinine levels after treatment among the different groups (Table 4).

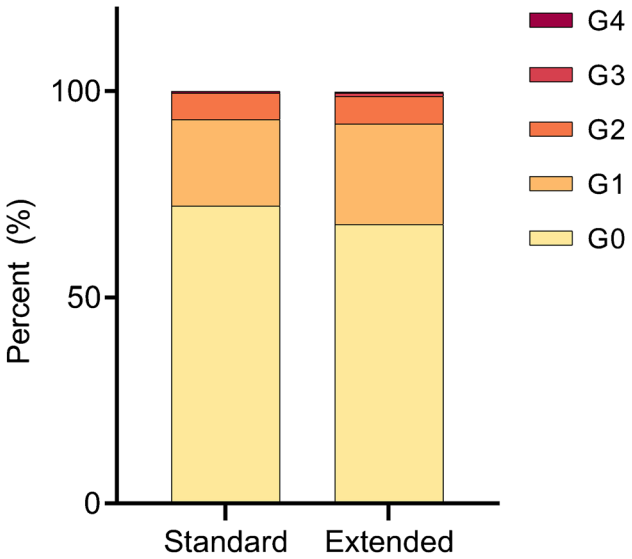

Fig. 1 Creatinine grading composition distribution of the two groups after treatment. In the standard group and the extended group, there are few G3 and G4 populations shown in the figure, and there is no significant difference in the proportion grade composition population between the two groups

Table 2 Comparison of post-treatment renal function between the standard and extended treatment groups

	Standard ($n=281$)		Extended ($n=356$)		
	Number (n)	Percent (%)	Number (n)	Percent (%)	P
Creatinine Grading					0.448
G0	203	72.2	241	67.7	
G1	59	21.0	87	24.4	
G2	18	6.4	24	6.7	
G3	0	0	3	0.8	
G4	1	0.4	1	0.3	
Creatinine	89.30 ± 51.19		93.20 ± 55.98		0.364

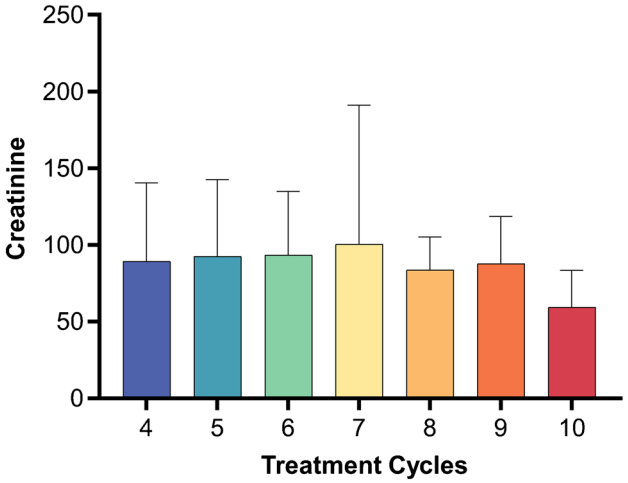

Fig. 2 Average creatinine value after different cycles of treatment (mean ± SD)

Total population survival analysis

As of the last date of follow-up, 362 patients were deceased, of which 222 patients died due to NET disease progression. The median follow-up time was 88.3 months (95% CI: 79.3–97.3). Median OS was 66.1 months (95% CI: 61.2–71.0) for the entire cohort, 52.8 months (95% CI: 45.5–60.2) for the four-cycle group, and 72.8 months (95% CI: 66.2–79.5) for the > 4-cycle group. Cox regression analysis indicated a better prognosis for the > 4-cycle group in terms of OS (HR: 0.580, $P < 0.001$) and DSS (HR: 0.599, $P < 0.001$) (Fig. 3).

Univariate and multivariate analysis of survival prognosis (OS) in NET patients treated with PRRT

Clinical features and treatment information that may affect the efficacy and prognosis of PRRT were analyzed. The results of the univariate analysis showed that age, primary site, type of radionuclide therapy, and more treatment cycles affect the OS of patients with NETs (Table 5). After adjusting for the multivariate analysis, we found that patients receiving extended treatment still had a better overall prognosis compared to those on the standard treatment ($P < 0.001$).

Analysis of more than 4 cycles of treatment in different subgroups

According to the results of univariate and multivariate analyses, the ^{177}Lu and combination treatment subgroups showed better prognoses, so we studied the effect of multiple treatments in these two subgroups by survival analysis.

Table 3 Renal function creatinine grade and value after different cycles of treatment

	Cycles 4 ($n=281$)	Cycles 5 ($n=151$)	Cycles 6 ($n=105$)	Cycles 7 ($n=65$)	Cycles 8 ($n=22$)	Cycles 9 ($n=10$)	Cycles 10 ($n=3$)
Creatinine Grading							
G0	203 (72.2)	104 (68.9)	72 (68.6)	41 (63.1)	15 (68.2)	7 (70.0)	2 (66.7)
G1	59 (21.0)	37 (24.5)	24 (22.9)	16 (24.6)	7 (31.8)	2 (20.0)	1 (33.3)
G2	18 (6.4)	7 (4.6)	9 (8.6)	7 (10.8)	0	1 (10.0)	0
G3	0	3 (2.0)	0	0	0	0	0
G4	1(0.4)	0	0	1(1.5)	0	0	0
Creatinine	89.3 ± 51.2(29.0, 701.0)	92.5 ± 50.2 (41.2, 425.7)	93.3 ± 41.5 (32.0, 317.0)	100.0 ± 91.7 (34.4, 779.0)	83.6 ± 21.57 (46.0, 131.9)	87.8 ± 30.69 (60.9, 165.1)	59.3 ± 24.3 (39.7, 86.4)

Table 4 Effect of therapeutic cumulative dose on renal function

	4 cycles	5, 6 cycles	7–10 cycles	*P*
^{177}Lu ($n=183$)	113	56	14	
Cumulative dose	26.2 ± 2.8 (16.5–31.4)	34.0 ± 4.9 (18.9–44.0)	49.6 ± 8.6 (39.3–64.1)	
Creatinine	89.6 ± 41.4	88.0 ± 36.6	86.2 ± 21.7	> 0.05
^{90}Y ($n=38$)	21	16	1	
Cumulative dose	11.5 ± 3.0 (6.5–15.6)	15.8 ± 3.0 (9.0–20.6)	/	
Creatinine	98.6 ± 40.2	110.9 ± 86.7	/	> 0.05
^{90}Y + ^{177}Lu ($n=416$)	147	184	85	
Cumulative dose	21.6 ± 4.5 (7.5–35.6)	28.7 ± 6.1 (13.6–42.2)	38.6 ± 8.8 (20.7–65.9)	
Creatinine	87.7 ± 58.9	92.7 ± 44.6	95.8 ± 80.7	> 0.05

Survival analysis results showed that in the ^{177}Lu treatment subgroup, the median survival time of OS and DSS in the multi-course treatment group was significantly longer than that in the standard treatment group (median OS, 91.8 mo vs. 56.8 mo, $P < 0.001$; median DSS, 120.3 mo vs. 77.0 mo, $P < 0.001$) (Fig. 4).

In the combined treatment subgroup, the median survival time of OS and DSS in the multi-course treatment group was also significantly higher than that in the standard treatment group (median OS, 73.0 mo *vs.* 53.6 mo, $P < 0.001$; median DSS, 91.0 mo vs. 79.4 mo, $P = 0.041$) (Fig. 5).

Discussion

Nephrotoxicity has consistently been a concerning issue of PRRT, posing significant constraints on therapy implementation and overall therapeutic outcomes. Many patients with NETs likely need additional treatment beyond the conventional quartet of PRRT cycles; there is a need for further comprehensive research into the occurrence and severity of PRRT-related nephrotoxicity, and subsequent patient-centric modifications need to be made to the current therapeutic strategies to ensure effective disease management without compromising renal safety.

Our analysis of nephrotoxicity indicated no significant difference in overall renal function between the standard four-cycle treatment group and the group treated with more than four cycles of PRRT. Additionally, we observed no correlation between rising creatinine levels and the number of treatment cycles, thereby underscoring the renal safety of additional PRRT cycles. These findings are consistent with a prior small-scale study of 15 patients, which suggested the safety of multiple [^{177}Lu]Lu-Octreotate treatments in NET patients and highlighted its potential to improve survival [16]. Our study, with its considerably larger patient cohort, corroborates and amplifies this initial evidence of the safety of more than four cycles of PRRT.

Regarding the therapeutic efficacy of PRRT, our study suggested an association between increased treatment cycles and improved treatment response in NET patients. In our retrospective analysis, patients who underwent more than four treatment cycles showed improved OS and DSS outcomes compared to those who received the standard four-cycle regimen. This association persisted after multivariate analysis adjustment, with multiple treatment courses continuing to exhibit a significant role in enhancing prognosis for patients with NETs. Tessa et al. reported improved remission rates in patients receiving a cumulative treatment dosage exceeding 22.2 GBq of PRRT, as compared to those receiving less than 22.2 GBq [17]. Similarly, our study saw an average cumulative dosage of 22.67 ± 5.39 GBq (range, 6.5–35.6 GBq) in the standard four-cycle treatment group, and a significantly higher average cumulative dosage of 32.10 ± 9.28 GBq (range, 9.0–65.9 GBq) in the group undergoing extended PRRT, without a corresponding significant difference in nephrotoxicity no matter which radionuclide was used, as measured by serum creatinine levels. These results suggest a potential paradigm shift in the management of NETs could be necessary, promoting a tailored approach where a higher number of treatment cycles might be beneficial for a subset of patients, thereby significantly improving disease prognosis.

We also observed differences in prognosis between the standard treatment group and the extended treatment group. Within both the sole ^{177}Lu treatment cohort and the combined treatment sub-cohort, the results suggested an association of better prognosis with extended treatment. An increased number of treatment cycles appeared to correlate with a better prognosis in our study, irrespective of whether the initial four cycles included ^{90}Y therapy or not. Both our univariate and multivariate analysis results indicated a trend of superior prognosis in the combined therapy group compared to the ^{177}Lu-only group. However, this trend did not reach statistical significance, potentially due to the inherent influence of disease staging on the choice of combined therapy. Our multivariate analysis revealed that NETs of the pancreas and thoracic had worse prognoses, which is consistent with earlier studies reporting differential prognostic profiles for NETs arising from different primary sites [18, 19].

While this study did not aim to specifically evaluate the risk of individual radionuclides, it cannot be omitted that a higher risk for nephrotoxicity compared with ^{177}Lu has been attributed to ^{90}Y, due to the longer tissue reach of the latter [3]. We did not find that increased frequency of ^{90}Y treatment significantly affected renal function (as shown in Table 4). However, this study is limited by the relatively

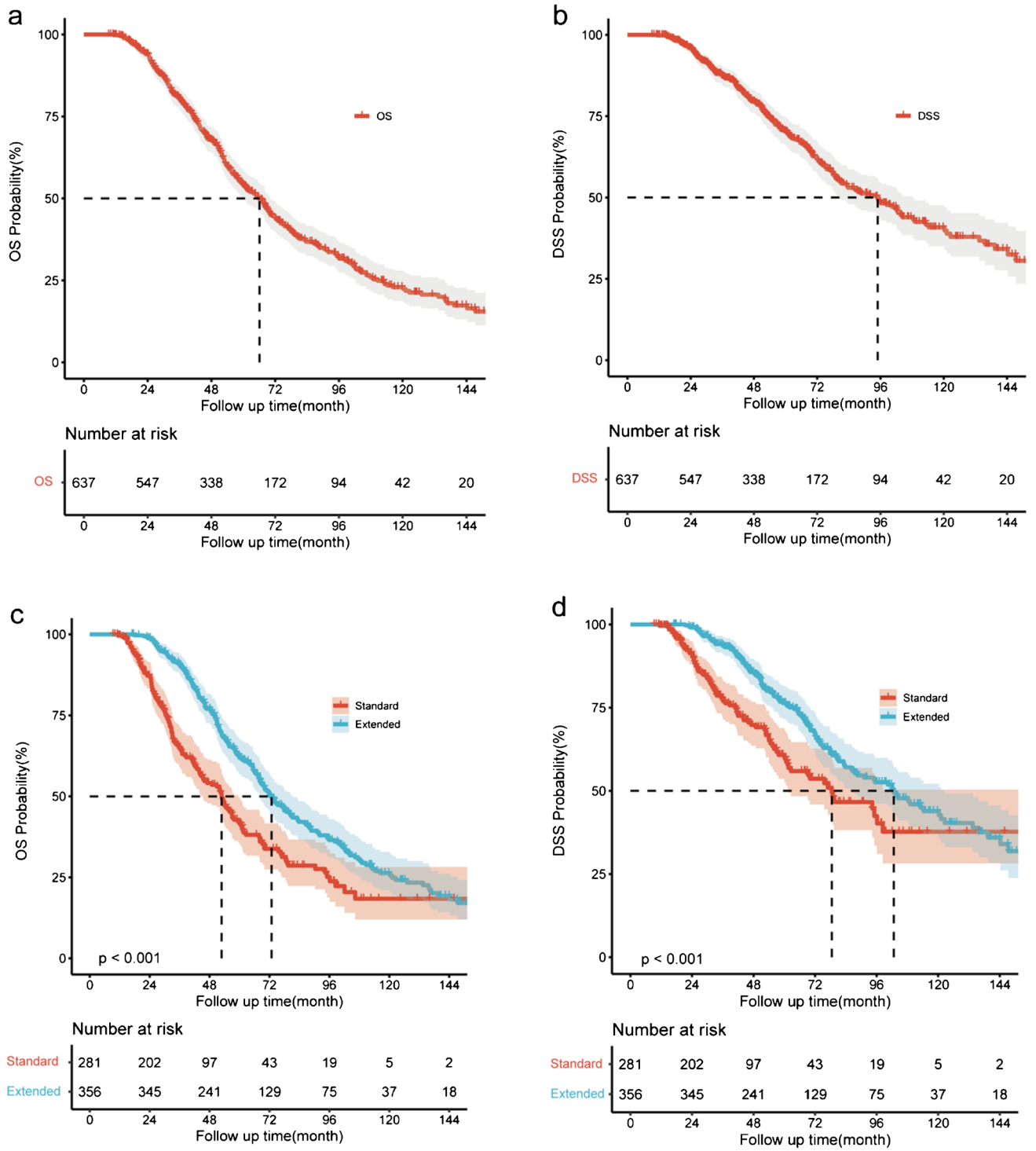

Fig. 3 Kaplan–Meier curves for OS and DSS (in months) from start of PRRT for all patients with overall population (**a**, **b**) and for subgroups with different numbers of treatment cycles (**c**, **d**). The Median OS was 66.1 months for the entire cohort, 52.8 months for the standard group, and 72.8 months for the extended group ($P < 0.001$). Median DSS was 94.9 months for the entire cohort, 78.5 months for the standard group, and 102.7 months for the extended group ($P < 0.001$)

small sample size of patients treated with ^{90}Y and its nature as a single-center retrospective study. Prospective, multi-center studies are naturally needed in the future for further verification of our findings. The maximum dose of ^{90}Y administered in a single dose and the total cumulative dose may also affect the results. Patient-specific dosimetry

Table 5 Univariate and multivariate analysis of survival prognosis in NETs treated with PRRT

	No. of Patients	Univariate analysis		Multivariate analysis	
		HR and 95% CI	*P*	HR and 95% CI	*P*
Age					
<60	297				
≥60	340	1.297 (1.053, 1.597)	0.014	1.354 (1.095, 1.674)	0.005
Gender					
Male	355				
Female	282	0.864 (0.701, 1.064)	0.169		
Primary site					
Pancreas	235				
Gastrointestinal	226	0.661 (0.520, 0.841)	0.001	0.618 (0.485, 0.787)	<0.001
Thoracic	53	1.327 (0.915, 1.926)	0.136	1.270 (0.874, 1.845)	0.211
Cup	82	0.751 (0.520, 1.085)	0.127	0.706 (0.487, 1.024)	0.067
Other	41	0.654 (0.410, 1.042)	0.074	0.506 (0.313, 0.818)	0.005
Radionuclides					
^{177}Lu	183				
^{90}Y	38	1.352 (0.876, 2.087)	0.173	1.282 (0.829, 1.981)	0.264
Combination	416	0.880 (0.689, 1.124)	0.306	0.924 (0.716, 1.192)	0.543
Cycles Group					
=4	281				
>4	356	0.580 (0.469, 0.718)	<0.001	0.550 (0.440, 0.686)	<0.001

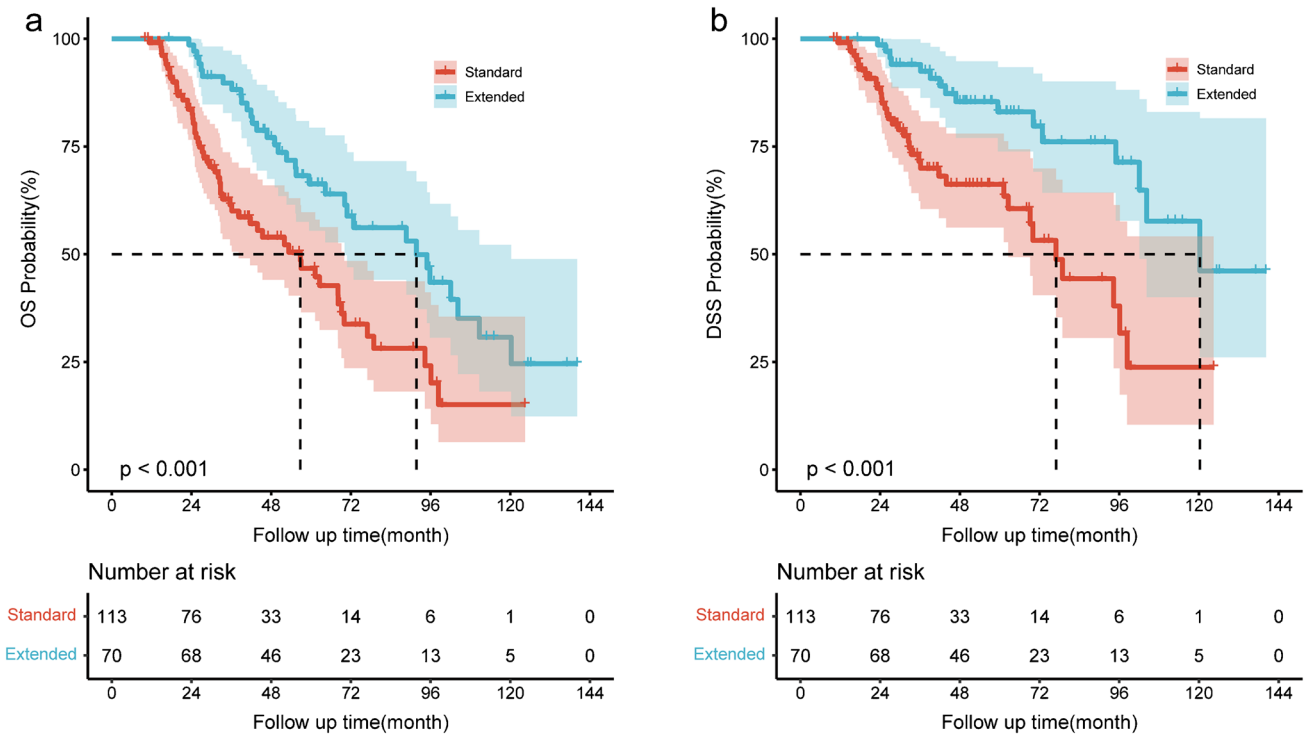

Fig. 4 Kaplan–Meier curves of OS (**a**) and DSS (**b**) for the.^{177}Lu treatment subgroup ($n=183$) stratified by treatment cycles. The median OS was 56.8 months for the standard group, and 91.8 months for the extended group ($P<0.001$). The median DSS was 77.0 months for the standard group, and 120.3 months for the extended group ($P<0.001$)

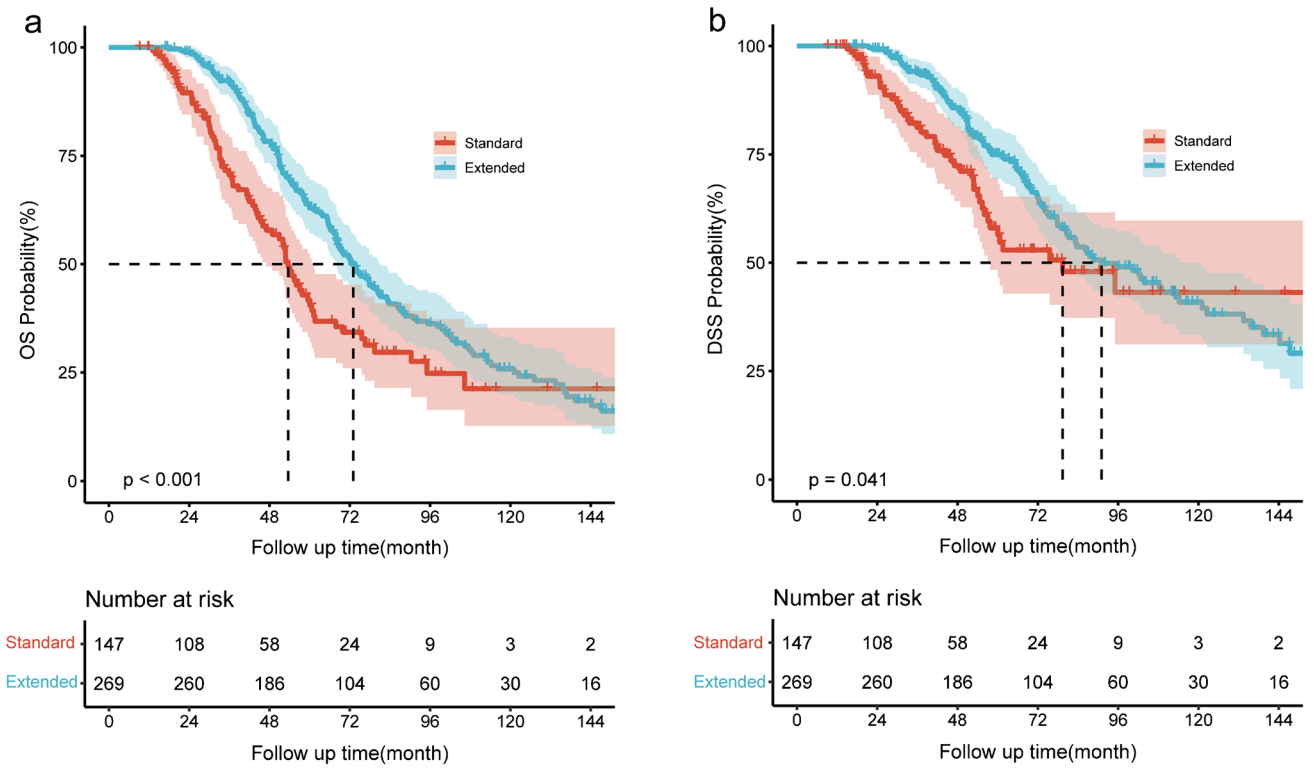

Fig. 5 Kaplan–Meier curves of OS (**a**) and DSS (**b**) for the combined treatment subgroup ($n=416$) stratified by treatment cycles. The median OS was 53.6 months for the standard group, and 73.0 months for the extended group ($P<0.001$). The median DSS was 79.4 months for the standard group, and 91.0 months for the extended group ($P=0.041$)

has been proposed as a method for mitigating risk [20]. Bodei et al. found in their analysis of 807 patients treated at their center that PRRT using ^{90}Y alone or in combination with ^{177}Lu had a higher risk of nephrotoxicity, 33.6% for ^{90}Y, 25.5% for combination therapy and 13.4% for ^{177}Lu; $P<0.0001$ [21]. In their study, no association was found between nephrotoxicity grade and duration of PRRT exposure, dosimetry had a limited ability to predict nephrotoxicity and other clinical factors were considered likely to be involved in the development of impaired kidney function. Stefano et al. reported that [^{90}Y]Y-DOTATOC followed by [^{177}Lu]Lu-DOTATATE treatment was both effective and safe [5]. In addition, compared to the single isotopic treatment of [^{90}Y]Y-DOTATATE, tandem radioisotopes (^{90}Y/^{177}Lu-DOTATATE) therapy has been by several other studies shown to offer an extended overall survival rate, with comparable safety profile making tandem therapy is a feasible and effective treatment choice for refractory NETs not amenable to standard treatment [22–24]. In our study, 17 patients underwent tandem therapy, including 7 from the standard treatment group and 10 from the group undergoing more than four cycles, and tandem treatment did not significantly affect nephrotoxicity. Predictive dosimetry was not performed, although co-infusion with amino acids was done for all patients.

The number of PRRT cycles each patient received was tailored based on their response to the treatment, disease progression, etc., survival was calculated from the start of PRRT, and we assumed that the prior treatments for both groups were comparable. However, we acknowledge that the potential synergistic effects between extended PRRT and previous treatments is worth exploring in the future, to further enhance the treatment outcomes for NET patients, such as PRRT in conjunction with immunotherapy [25] or chemotherapy [26]; such investigations could provide invaluable insights into optimizing therapeutic strategies and improving patient care in the long term. The use of alpha-emitting radionuclide ^{225}Ac may also ameliorate the prognosis for treatment-refractory NET patients [27]. Moreover, strategies to prolong tumor retention time might further augment the efficacy of tumor treatments. For example, extending the drug's dwell time at the tumor site through the conjugation of DOTATATE with EB could potentially enhance therapeutic effects. Preliminary findings reported by Chen et al. have attested to the effectiveness of this approach and its safety regarding nephrotoxicity with or without amino acid protection [28–30].

Although this study has a large, long-term follow-up study sample, it remains limited by its retrospective nature. Therefore, in addition to the discussion above, the following limitations also need to be mentioned. First, we cannot exclude that the observed association is causal, and although we tried our best to control confounding factors and conduct comparative analysis of differences at the baseline level, there may still be confounding factors that we have not considered, and our study only included data from one center. In the future, prospective and large-scale randomized controlled studies with larger samples and more extensive renal function assessments are needed to further determine the safe dose of PRRT.

Conclusion

In conclusion, our research constitutes a significant step forward in supporting the safety and efficacy associated with administering more than four cycles of PRRT for NET patients. These insights contribute to shaping more personalized, targeted, and effective therapeutic strategies, thereby improving survival and disease prognosis.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all participants included in the study.

Competing interests The authors declare no competing interests.

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