# Analysis of outcome in patients with different primary localisation of neuroendocrine tumors after PRRT. 10 years single institution experience

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## Abstract

**Objective:** The aim of this retrospective study is to analyze the outcome and survival of patients with well-differentiated metastatic neuroendocrine neoplasm (NEN) treated with peptide receptor radionuclide therapy (PRRT). **Subjects and Methods:** The treatment was applied to 32 subjects, 18 men and 14 women, aged 39-79 years (median 65 years). The dominant grade of the tumor according to the Ki-67 index was G2 (75%) compared to G1 (25%). The average number of three-day protocol PRRT cycles was 4 (1.00-9.00). Lutetium-177- DOTA$^{0}$,Tyr$^{3}$,Thr$^{8}$-octreotide ($^{177}$Lu-DOTA-TATE) was used in 22 (69%), both $^{177}$Lu-DOTA-TATE and yttrium-90-DOTA$^{0}$,Tyr$^{3}$-octreotide ($^{90}$Y-DOTA-TOC) in 8 (25%), and $^{90}$Y-DOTA-TOC in 2 (6%) patients. No adverse effects of PRRT were recorded excerpt one patient who has died soon after the first therapy due to ileus after surgery. **Results:** Response to PRRT according to response evaluation criteria in solid tumors (RECIST) 1.1. criteria showed that 9 (28%) patients had disease progression, 16 (50%) had stable disease, and 7 (22%) had partial remission. Significantly shorter time until progression or death of 18 months was detected for patients with disease progression than for other groups with stable disease (34.5 months, $P<0.02$) and partial remission (35 months, $P<0.05$). However, the values obtained for overall survival were not significantly different between the studied groups being 33 months in subjects with disease progression, and 34.5 and 35 months in groups with stable disease and partial remission, respectively. In 6 subjects, an asymptomatic low hemoglobin level was detected that did not require intervention (Grade1). In 2 subjects, nephrotoxicity occurred with glomerular filtration rate (GFR) values below 30mL/min/1.73m$^2$ (Grade3). **Conclusions:** It can be concluded that PRRT according to a three-day nephroprotection protocol is a reliable and safe method of treatment for advanced NEN. Longer time to disease progression and overall survival in most patients underline the great potential of this treatment method in patients with advanced NEN.

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## Introduction

Neuroendocrine neoplasms (NEN) are a heterogeneous group of tumors arising from diffuse, pluripotent neuroendocrine cells. Despite the fact that neuroendocrine cells are anatomically independent and do not form separate organs, they constitute a functional system, the so-called diffuse neuroendocrine system, with specific biochemical, cytological, and secretory properties. The most common localization of NEN is in the digestive tract-gastroenteropancreatic (GEP)-and the lungs [1, 2]. Immunohistochemical confirmation of neuroendocrine differentiation is based on the expression of chromogranin A and CD56, while tumor aggressiveness is characterized by evaluation of the Ki-67 proliferation index [3]. Elucidation of genetic and molecular mechanisms involved in NEN pathogenesis, together with tumor heterogeneity and specific molecular features, may provide new possibilities for diagnosis and therapy [4].

Neuroendocrine neoplasms represent a major diagnostic challenge due to their late, nonspecific, and variable clinical presentation, often accompanied by early development of liver metastases. When NEN are suspected, it is essential to identify the primary tumor localization and assess the presence of regional and distant metastases [5]. Imaging techniques play a key role in diagnosis, staging, treatment selection, and follow-up of patients with NEN. Radiological imaging methods are usually the first diagnostic approach for tumor detection [5, 6].

Molecular imaging techniques provide information on the expression of various receptors overexpressed in NEN, particularly somatostatin receptor (SSTR) status asses-

sed by somatostatin receptor scintigraphy, as well as metabolic activity evaluated using fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET). Overexpression of somatostatin receptors represents a molecular target enabling both imaging with radiopharmaceuticals and treatment using therapeutic radionuclides according to the theranostic principle [5, 6].

Treatment of these tumors represents a major challenge, with limited and often palliative options for patients with metastatic disease [1]. Peptide receptor radionuclide therapy (PRRT) is a targeted molecular therapy involving systemic administration of radiopharmaceuticals with high affinity for somatostatin receptors, particularly subtype 2, which are overexpressed in neuroendocrine tumors. Radionuclide-labeled somatostatin receptor agonists yttrium-90-DOTA$^0$,Tyr$^3$-octreotide ($^{90}$Y-DOTA-TOC) and lutetium-177-DOTA$^0$,Tyr$^3$,Thr$^8$-octreotide ($^{177}$Lu-DOTA-TATE) or $^{177}$Lu-DOTA$^0$,Tyr$^3$-octreotide have been successfully used for more than two decades in the treatment of metastatic or inoperable neuroendocrine neoplasms expressing somatostatin receptor subtype 2 [7-11].

The aim of this study was to analyze treatment outcome and survival of patients with well-differentiated metastatic NEN treated with PRRT performed at a single institution over a 10-year period.

## Subjects and Methods

### Patients

During the last decade, a total of 37 patients were referred to the Center for Nuclear Medicine, University Clinical Center Niš, for continuation of treatment of neuroendocrine tumors. Of these, five patients were excluded based on criteria defined in relevant guidelines [11], including hydronephrosis of a single kidney, severe cardiovascular disease with heart failure, secretory active insulinoma with persistent hypoglycemia, and Karnofsky Performance Status of 20%.

Treatment was applied to 32 subjects aged 39-79 years (median 65 years), including 18 men and 14 women, in whom a neuroendocrine tumor had been previously confirmed immunohistochemically. The proliferative Ki-67 index of tumors ranged from 0.10% to 18.50%, and the dominant tumor grade according to the Ki-67 index was G2 (75%) compared with G1 (25%) [4].

The most common primary tumor localization was the gastrointestinal tract (75%, 24 patients), while lung NET were present in three subjects and other localizations in five subjects (16%). In 17 subjects, NET were functionally inactive, while in the remaining patients tumors were hormonally active. Post-treatment follow-up was performed for at least 24 months after the last PRRT cycle.

This study (10413/13) was approved by the Ethics Committee of the University Clinical Center Niš. All patients provided written informed consent for diagnostic and therapeutic procedures, as well as for retrospective scientific analysis of their data.

### Imaging of SSTR status

Somatostatin receptor expression status and disease extent were assessed using somatostatin receptor scintigraphy with the radiopharmaceutical technetium-99m-($^{99m}$Tc)-Tektrotyd (HYNIC-[D-Phe$^1$,Tyr$^3$-octreotide], POLATOM, Poland). Radiochemical purity was assessed using thin-layer chromatography and exceeded 95%.

Post-therapy scintigraphy was performed 24-48 hours after therapy with peptides labeled with $^{177}$Lu-DOTA-TATE, while after therapy with $^{90}$Y-DOTA-TOC only bremsstrahlung imaging was performed.

Scan interpretation was qualitative and performed according to the Krenning score [10].

### Peptide receptor radionuclide therapy (PRRT)

Peptide receptor radionuclide therapy was applied in all subjects as monotherapy using radionuclide-labeled somatostatin receptor agonists $^{90}$Y-DOTA-TOC (POLATOM, Poland) or $^{177}$Lu-DOTA-TATE (POLATOM, Poland; ITM Isotope Technologies Munich), or as tandem therapy. In patients with radiologically proven bulky lesions over 2cm in diameter, $^{90}$Y-DOTA-TOC was used either alone or in combination with $^{177}$Lu DOTA-TATE as tandem therapy [11]. The administered activity per cycle was 5.55GBq [11].

After completion of the first PRRT, patients were followed up with regular cross-sectional imaging at 4-6 month intervals. If there was evidence of disease progression, the issue was revisited at a multidisciplinary team meeting that suggested retreatment with PRRT after a previous somatostatin receptor scintigraphy [12].

A three-day protocol was applied, during which the patients received nephroprotective amino acids. The minimum interval between PRRT cycles was eight weeks. The median number of applied cycles was four, with a cumulative activity of 22.2GBq. Renal protection during PRRT involved co-infusion of amino acid solutions according to established protocols [9, 11].

Most patients tolerated PRRT well. During or after therapy, nephrotoxicity was observed in 4 patients, while hematotoxicity was present in 6 patients. One patient died after the first treatment due to postoperative ileus.

### Follow-up

Treatment response was assessed using computed tomography (CT) or magnetic resonance imaging (MRI) according to response evaluation criteria in solid tumors (RECIST) 1.1 criteria [13, 14]. Functional imaging using somatostatin receptor scintigraphy with $^{99m}$Tc-Tektrotyd (Krenning score) was performed before and after therapy [10].

Based on RECIST 1.1 criteria, patients were classified into three groups: progressive disease (PD), stable disease (SD), and partial remission (PR). No patient achieved complete remission according to RECIST 1.1 criteria.

Progression-free survival (PFS) and overall survival (OS) were defined as primary endpoints. Progression-free survival was defined as the time from initiation of PRRT until disease progression or death from any cause. Overall survival was defined as the time from the first PRRT cycle until death from any cause or last follow-up.

### Analysis of side effects of PRRT

In all patients, a complete blood count analysis as well as biochemical parameters related to liver and kidney function and complete electrolyte status was regularly performed at regular time intervals that included the period before therapy, one month after therapy, and 3-6 months after the end of the PRRT cycle.

Baseline cratinine clearance (CCl) as the measure of glomerular filtration rate greater than 60mL/min/1.73m$^2$ was mandatory before enrolling patients for PRRT. These values were monitored for each patient at each follow-up point [12].

### Statistical analyses

Statistical analyses were performed using SPSS version 18.0. Data are presented as mean, median, range, or number and percentage.

Comparison of proportions between independent groups was performed using the Chi-square test or Fisher's exact test. Comparisons within the same subjects between baseline and post-treatment measurements were performed using McNemar's test. The Shapiro-Wilk test was used to assess normality of distribution.

Due to significant deviations from normal distribution, non-parametric tests were applied. Kaplan-Meier survival analysis with the generalized Wilcoxon test was used for time-to-event analysis. The Kruskal-Wallis test was used for comparison among three groups, followed by post hoc Mann-Whitney tests. The Wilcoxon signed-rank test was used for paired comparisons. ANOVA analysis of variance was used to test quantitative dependent variables by a single factor. General linear model (GLM) multivariate analysis model was used to test the different factors that can influence the outcome. Statistical significance was set at $P<0.05$.

## Results

### Characteristics of patients and applied treatment

In this retrospective analysis, PRRT outcomes were evaluated in 32 patients with metastatic NEN (Table 1).

Gastroenteropancreatic tumors were the most common primary localization (75%, $P<0.001$), followed by bronchopulmonary NEN (9%) and other localizations (16%). Non-functioning tumors were present in 17 patients (53%), while 15 patients (47%) had functioning tumors. Tumor grade G2 was significantly more frequent than G1 (75% vs. 25%, $P<0.005$).

Multiple metastatic sites were present in 62% of patients ($P<0.05$), while isolated liver metastases were present in 28%. The Krenning score was grade 3 in 14 patients and grade 4 in 18 patients.

A total of 124 therapeutic cycles were administered. Peptide receptor radionuclide therapy was repeated after disease progression in six patients. The administered cumulative activity ranged from 5.55 to 49.95GBq per patient (mean 22.2±11.3GBq).

Previous treatments included surgery and biological therapy in 14 patients (44%), combined therapies in 12 patients (37%), and surgery alone in six patients (19%). Peptide receptor radionuclide therapy was the first treatment option for only one out of the 6 patients due to an inoperable tumor of large dimensions; following tumor volume reduction, this patient was successfully operated on. The average number of PRRT cycles was 4 (1.00-9.00). Lutetium-177-DOTA-TATE was used in 22 patients (69%), combined $^{177}$Lu-DOTA-TATE and $^{90}$Y-DOTA-TOC therapy was applied in 8 patients (25%), and $^{90}$Y-DOTA-TOC alone was used in 2 patients (6%).

***Table 1.*** *Demographic data, extent of disease and treatment of patients with NEN.*

| | |
|---|---|
| **Gender (number)** | |
| Male | 18 |
| Female | 14 |
| **Age (years)** | 62.4±10.1 (39-79) |
| **Primary tumor site** | |
| Gastroenteropancreatic | 24 |
| Lung | 3 |
| Other | 5 |
| **Hormonal activity** | |
| Non-functional | 17 |
| Functional | 15 |
| **Ki-67 index (%)** | |
| <2 | 8 |
| 3-20 | 24 |
| >20 | - |
| **Metastases** | |
| Liver | 9 |
| Bones | 1 |
| Lung | 1 |
| Lymph nodes | 1 |
| Multiple sites | 20 |
| **Krenning score** | |
| 3 | 14 |
| 4 | 18 |
| **Previous treatment** | |
| Surgery and biological therapy | 14 |
| Chemotherapy and/or RFA | 12 |
| Surgery | 5 |
| Surgery after PRRT | 1 |
| **Number of cycles** | |
| One PRRT | 26 |
| PRRT retreatment | 6 |
| **Cumulative activity delivered by PRRT per patient (GBq)** | 5.55-49.95 |

*NEN, neuroendocrine neoplasms; RFA, radiofrequency ablation; PRRT, peptide receptor radionuclide therapy*

## Response to PRRT

Response to PRRT according to RECIST 1.1 criteria showed that 9 patients (28%) had disease progression, 16 patients (50%) had stable disease, and 7 patients (22%) had partial remission (Table 2). The largest number of subjects who achieved partial remission was males, although this difference did not reach statistical significance. Significant differences between the compared groups were detected for the Ki-67 index ($P<0.05$), tumor grade ($P<0.05$), and incidence of partial disease remission based on scintigraphic findings ($P< 0.05$).

Post hoc comparisons showed that Ki-67 index values were significantly higher in patients with disease progression than in those with stable disease (10.00 vs. 3.75%; Mann-Whitney test, $P<0.05$). In addition, G2 tumors were significantly more frequent in patients with disease progression compared with those with stable disease (100.0% vs. 56.25%; Fisher's exact test, $P<0.05$).

The results indicate higher tumor grade are associated with poorer outcome and disease progression, while the number of PRRT cycles has no statistically significant impact on treatment outcome.

Scintigraphic findings were to a lesser extent consistent with radiological imaging findings used for disease assessment; however, a considerable number of subjects were classified as having stable disease by both scintigraphy and radiological examinations. Complete remission was detected by scintigraphy in five subjects. According to RECIST 1.1 criteria, among these five patients, one was classified as having disease progression, three as having stable disease, and one as having partial remission (Figure 1).

Table 3 and Figure 2 show differences in PFS and OS among groups of patients with different outcomes after completion of PRRT at the end of the observation period. Multiple comparisons using the Mann-Whitney test showed a significantly shorter time to progression or death of 18 months in patients with disease progression compared with patients with stable disease (34.5 months, $P<0.02$) and partial remission (35 months, $P<0.05$). An identical finding for PFS was obtained using the generalized Wilcoxon test in the Kaplan-Meier analysis shown in Figure 2 (left panel). However, OS values were not significantly different between the studied groups during the observation period (Table 3 and Figure 2, right panel). Overall survival was 33 months in patients with disease progression and 34.5 and 35 months in patients with stable disease and partial remission, respectively.

Table 4 shows the multivariate analysis of PFS and OS values as well as outcomes based on RECIST 1.1 criteria in relation to the tested variables that could independently or in combination with other variables influence the outcome of treatment. Differences in the mean values of the variables were also tested. PFS and OS values were not significantly different between male and female subjects, between patients with G1 and G2 stage NEN. There was no difference in PFS and OS in relation to the primary localization of the tumor as

***Table 2.*** *Comparison of NEN patients characteristics, SSTR scintigraphy and number of PRRT cycles in relation to disease outcome.*

| Variables | RECIST 1.1 status | | | P |
|---|---|---|---|---|
| | Progression (n=9) | Stable disease (n=16) | Partial remission (n=7) | |
| **Sex, n (%)** | | | | |
| Male | 2 (22%) | 11 (69%) | 5 (71%) | 0.052 |
| Female | 7 (78%) | 5 (31%) | 2 (29%) | |
| **Number of patients and range of Ki-67 index (%)** | 4 (1.5-11.0) | 18 (0.2-18.50) | 10 (0.1-13.00) | n.s |
| **Grade, n (%)** | | | | |
| Grade 1 | 0 (0.0%)* | 7 (44%) | 1 (14%) | 0.040 |
| Grade 2 | 9 (100.0%) | 9 (56%) | 6 (86%) | |
| **Number of cycles** | 1.00 (1.00-2.00) | 1.00 (1.00-2.00) | 1.00 (1.00-1.00) | n.s. |
| **Scintigraphic status** | | | | |
| Progression | 1 (11%) | 1 (6%) | 0 (0%) | 0.043 |
| Stable disease | 7 (78%) | 11 (69%) | 2 (29%) | |
| Partial remission | 0 | 1 (6%) | 4 (57%) | |
| Complete remission | 1 (11%) | 3 (19%) | 1 (14%) | |

*NEN, neuroendocrine neoplasm; SSTR, somatostatin receptor; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors. * Progression vs Stable disease*

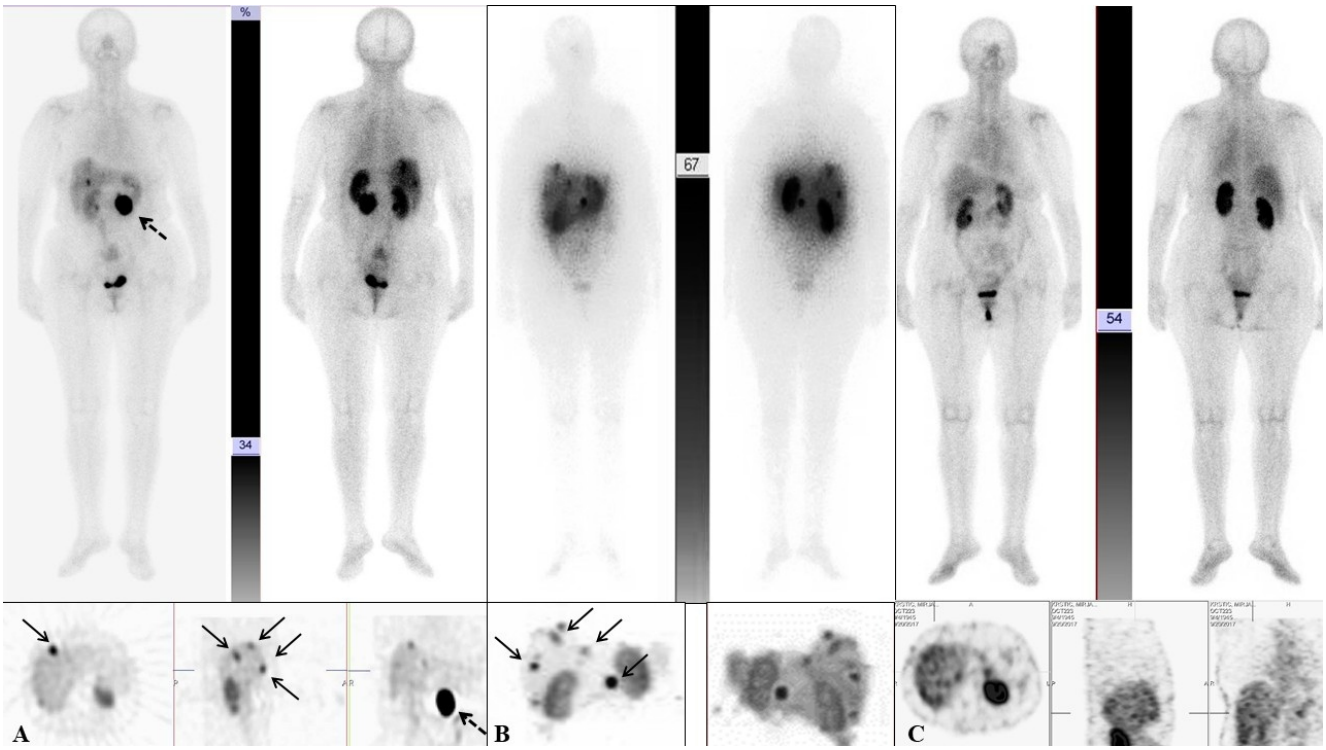


**Figure 1.** Whole body diagnostic scan and SPECT in patient with insulinoma (dotted arrow) and liver metastases (solid arrow)-NEN G2. A: Diagnostic scan with $^{99m}$Tc-Tektrotyd clearly delineating the primary lesion and numerous metastases in the liver. B: Posttherapy scan with $^{177}$Lu-DOTA-TATE after the surgery of primary tumor and first PRRT demonstrate multiple liver lesions. C: Control $^{99m}$Tc-Tektrotyd scan following PRRT shows complete resolution of all liver lesions.

***Table 3.*** *PRRT benefits in NENs patients*

| PRRT outcome | RECIST 1.1 evaluation | | | P |
|---|---|---|---|---|
| | Progression (n=9) | Stable disease (n=16) | Partial remission (n=7) | |
| Progression-free survival (months) | 18.00 (5.00-77.00)*,** | 34.50 (11.00-53.00) | 35.00 (29.00-48.00) | 0.020 |
| Overall survival (months) | 33.00 (7.00-122.00) | 34.50 (11.00-75.00) | 35.00 (29.00-48.00) | n.s. |

*PRRT, peptide receptor radionuclide therapy; NEN, neuroendocrine neoplasm; RECIST, Response Evaluation Criteria in Solid Tumors. * Progression vs Stable disease; ** Progression vs Partial remission.*

well as in patients with different localization of metastases. Significantly longer OS was in patients with a repeated cycle of PRRT amounting to an average of 76 months compared to those who received only one cycle of PRRT in which the survival was 32 months (P<0.001). Multivariate analysis showed that female gender as well as a higher degree of NET was associated with a significantly worse disease outcome, while patients who received a repeated cycle of PRRT had a significantly higher PFS and OS compared to those who received only one cycle of treatment (P<0.01).

### Toxicity of PRRT

In 6 subjects, an asymptomatic low hemoglobin level was detected that did not require intervention (Grade 1) [12]. In 2 subjects, nephrotoxicity occurred with GFR values below 30 ml/min/1.73m$^2$ (Grade 3) [12]. In one subject, PRRT was discontinued due to weakening of renal function after two received therapies, while in one subject, weakening of renal function occurred during follow-up and after a repeated cycle of PRRT (received a total of 9 doses in 2 cycles of PRRT).

## Discussion

In terms of epidemiological data, the incidence and prevalence of neuroendocrine neoplasms is increasing worldwide

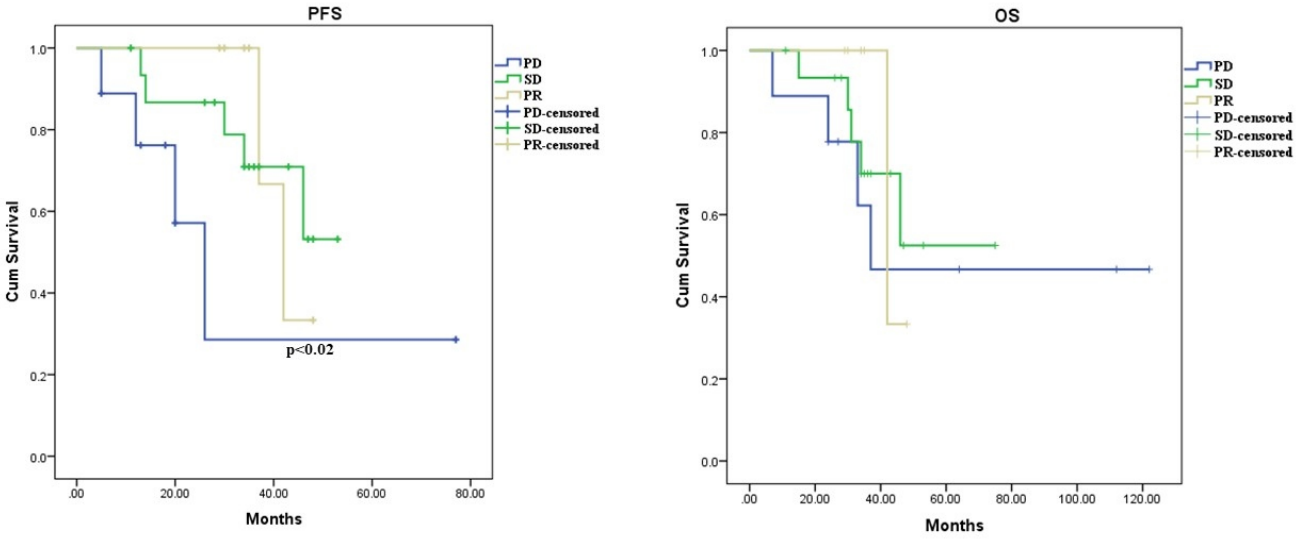


**Figure 2.** Kaplan-Meier analysis of PFS and OS in study groups based on RECIST 1.1 criteria. PD-progressive disease, SD-stable disease, PR-partial remission.

***Table 4.*** *Multivariate analysis of variables associated with outcome after PRRT*

| Variables | Categories | | | | | | |
|---|---|---|---|---|---|---|---|
| | Number | Mean PFS (months) | Mean OS (months) | Outcome (number of patients) | | | P |
| | | | | Progression | Stable disease | Partial remission | |
| **Sex** | | | | | | | |
| Male | 18 | 31.9±10.9 | 39.7±22.4 | 2 | 11 | 5 | 0.009 |
| Female | 14 | 29.3±20.6 | 41.0±27.2 | 7 | 5 | 2 | |
| **WHO Grade** | | | | | | | |
| G1 | 26 | 29.8±13.4 | 43.1±14.2 | 0 | 7 | 1 | 0.02 |
| G2 | 6 | 22.5±9.2 | 39.4±26.9 | 9 | 9 | 6 | |
| **Number of cycles** | | | | | | | |
| One PRRT | 26 | 28.8±13.4 | 32.1-10.7 | 5 | 14 | 7 | 0.01 |
| PRRT retreatment | 6 | 39.1±22.5 | 76.0±34.5* | 4 | 2 | 0 | |
| **Primary localisation** | | | | | | | |
| GEP | 24 | 29.3±16.6 | 42.0±27.1 | 9 | 10 | 5 | n.s |
| Lung | 3 | 32.6±21.0 | 37.6±21.0 | 0 | 3 | 0 | |
| Other | 5 | 36.5±15.6 | 36.6±5.8 | 0 | 3 | 2 | |
| **Metastases** | | | | | | | |
| Liver | 9 | 27.4±16.8 | 33.02±11.0 | 3 | 4 | 2 | n.s |
| Multiple organs | 20 | 30.5±15.3 | 38.9±21.9 | 6 | 9 | 5 | |
| Bones | 1 | 30.0 | 30.0 | 0 | 1 | 0 | |
| Lung | 1 | 53.0 | 53.0 | 0 | 1 | 0 | |
| Lymph nodes | 1 | 46.0 | 46.0 | 0 | 1 | 0 | |

**Anova significance: p<0.001, n.s: not significant*

[3]; however, differences in incidence between women and men have also been reported. Women are more likely to develop NEN of the appendix, stomach and cecum, while men more frequently develop NEN of the ileum and rectum [13]. A study showed that the incidence of gastroenteropancreatic NEN increased from 1.09 per 100,000 per year in 1973 to 6.98 per 100,000 per year in 2012 [2].

In our study, a higher frequency of men with NEN was observed, although without statistical significance compared to women. Although the sample size of this study is limited for epidemiological conclusions, 75% of patients were treated for metastatic NEN of gastroenteropancreatic origin, which is consistent with literature data reporting this localization as the most frequent. The majority of patients had G2 tumors. Our results demonstrated that a higher Ki-67 index and higher tumor grade are associated with poorer outcomes and disease progression. At the time of diagnosis, 62% of our patients had widespread metastatic disease involving multiple organs. This finding is consistent with previous studies emphasizing that nonspecific symptomatology of NEN represents a major obstacle for early diagnosis [3]. It has been reported that the average time from symptom onset to diagnosis is approximately 53.8 months, with symptoms often misinterpreted as functional gastrointestinal disorders [3].

Our study highlights differences between functional and morphological imaging modalities in the evaluation of treatment response in NEN patients. Nevertheless, in the majority of cases, imaging findings were concordant. A significant number of patients were classified as having stable disease by both scintigraphy and radiological imaging. However, complete remission was detected by scintigraphy in five patients, while none fulfilled complete remission criteria according to RECIST 1.1. Based on RECIST 1.1 criteria, among these five patients, one was classified as having disease progression, three as stable disease, and one as partial remission.

Only a limited number of studies have analyzed discrepancies between morphological and functional imaging methods in response assessment of NEN treatment [14]. One of the main reasons for these discrepancies lies in tumor heterogeneity and uneven receptor distribution. In addition, NEN often demonstrate disease stabilization rather than marked tumor shrinkage. Radiological techniques based on RECIST 1.1 criteria have limited sensitivity in slow-growing tumors and may be influenced by inflammatory changes leading to pseudoprogression [15]. Functional imaging based on somatostatin receptor visualization is highly sensitive, but lacks standardized quantitative parameters for precise response assessment. Therefore, combined functional and morphological imaging remains essential for accurate evaluation of treatment outcomes.

The optimal treatment of NEN is surgical resection at an early stage, before the development of regional or distant metastases, followed by additional therapeutic options including somatostatin analogues, chemotherapy, immunotherapy, mTOR inhibitors, and radiation therapy. Unfortunately, many patients are diagnosed at an advanced stage when curative treatment is no longer possible. Resection of the primary tumor aims to prevent complications such as bleeding or bowel obstruction [16]. Even in the presence of liver metastases, removal of the primary tumor has been shown to improve survival [17].

Supportive and palliative therapies, including pain control, play an important role in the management of NEN patients. These treatment modalities are not mutually exclusive and should be optimally sequenced by an experienced multidisciplinary team to maximize benefit and minimize adverse effects [18]. Peptide receptor radionuclide therapy using beta-emitting radiolabeled somatostatin analogues has significantly advanced systemic treatment of NEN over the past decades [16].

A meta-analysis including 22 studies with 1,758 patients with unresectable or metastatic NEN treated with $^{177}$Lu-labeled peptides reported an objective response rate of 33% and disease control rates of 79% according to RECIST criteria and 83% according to RECIST 1.1 criteria [7].

In the phase III clinical study NETTER-1, designed to examine the efficacy of PRRT with $^{177}$Lu-DOTA-TATE in patients with advanced SSTR-positive G1/G2 NEN of the midgut, survival longer than 20 months was observed in 65.2% of patients receiving radiopharmaceutical therapy, compared with only 10.8% of patients receiving high-dose cold octreotide. Response to therapy, measured as partial or complete response, was observed in 18% of patients in the lutetium group, compared with 3% of patients in the octreotide group [8, 9].

The results of another clinical study involving over 200 patients treated with $^{177}$Lu-DOTA-TATE showed improvement in quality of life and disease-related symptoms in 40%–70% of patients compared with a control group receiving high-dose cold octreotide [8]. In this study, the time to disease progression in patients treated with lutetium was 28.4 months, compared with 8.5 months in patients receiving octreotide alone [8].

Our results are comparable with those obtained in other studies. Peptide receptor radionuclide therapy was administered as a second- or third-line therapy in the majority of patients in our study group. In only one patient, PRRT was used as a first-line treatment to reduce the size of an inoperable tumor. In almost 72% of cases, disease control, stable disease, or partial remission was achieved, and the time to PFS was similar in both groups (34.50 months and 35.00 months, respectively) [6-8]. Also, our study found no significant differences in PFS and OS between genders, between patients with G1 and G2 tumor stage, nor in relation to the primary localization of the tumor and the site of metastases. There was a significant difference in survival in patients who received a repeated cycle of PRRT, averaging 76 months, compared to those who received only one treatment cycle, in which OS was an average of 34 months. Similar results were obtained in a study that analyzed 47 patients in whom the cycle of PRRT was repeated, where the OS was 71 months from the start of the first cycle [19]. By analyzing the individual effects of different variables as well as their combination on the outcome of the disease itself, our work showed that female gender as well as a higher degree of NET are associated with a significantly less favorable outcome of the disease, while patients who underwent a repeated cycle of PRRT had a more favorable survival outcome compared to those who received only one cycle of treatment. The results of our work showed

that PRRT is a safe procedure because hematotoxicity in our subjects was asymptomatic and negligible, detected in 6 out of 32 subjects and did not require treatment. Grade 3 nephrotoxicity was detected in only 2 out of 32 subjects, and in one subject after a repeated cycle of PRRT treatment. Grade 3 nephrotoxicity was detected in only 2 out of 32 subjects.

From the perspective of a multidisciplinary approach, PRRT can be of great benefit as neoadjuvant therapy, serving as a first step toward suppressing tumor spread and preparing the patient for surgery. Supportive treatment modalities, including PRRT, should be selected and administered in the correct sequence by an experienced multidisciplinary team. This approach should provide the greatest benefit, minimize risks and side effects, and ensure the best possible quality of life for the patient [18]. Neoadjuvant PRRT was successfully applied in one of our patients for shrinkage of a large tumor mass followed by surgical resection.

Treatment of NEN remains a major therapeutic challenge, and PRRT represents only one component within a spectrum of available treatment modalities. Somatostatin analogues are most often used as initial systemic therapy for disease control, symptom reduction, and antiproliferative effects [18]. Long-acting octreotide or lanreotide formulations are commonly used [18]. In our study cohort, the largest number of patients (n=14) received biological therapy with somatostatin analogues as first-line treatment, while 12 patients received cytotoxic chemotherapy based on streptozocin-fluorouracil or doxorubicin combinations. Although cytotoxic chemotherapy is recommended for more aggressive NEN, it is also indicated in advanced disease. This approach was previously considered the standard therapeutic option for advanced and unresectable NEN. However, studies have demonstrated relatively low response rates accompanied by significant toxicity [20, 21]. More recently, cytotoxic regimens have largely been replaced by the combination of capecitabine and temozolomide (CAPTEM), which has become the standard dual therapy for advanced NEN following publication of the ECOG-ACRIN E2211 study. This study demonstrated a significantly higher response rate and prolonged time to disease progression of 22.7 months, although treatment-related toxicity remained substantial [22].

Molecularly targeted therapies have significantly improved the management of NEN, particularly in advanced disease. Following the phase III RADIANT clinical trials, favorable outcomes were reported for everolimus, an oral inhibitor of the mechanistic target of rapamycin (mTOR) pathway [23]. In patients with progressive NET, particularly pancreatic NET, everolimus significantly improved progression-free survival compared with placebo (median PFS approximately 11 months vs. 4 months). Subsequently, the indication for everolimus was expanded to extrapancreatic NEN, including lung and gastrointestinal primaries, as demonstrated in the RADIANT-4 trial, establishing everolimus as a standard second-line therapy for nonfunctioning NET subtypes [24].

Cytoreductive procedures have also proven useful in the management of functionally active tumors, employing various techniques such as transarterial chemoembolization, transarterial embolization, radiofrequency ablation, and selective internal radiation therapy (SIRT) [25]. These procedures should be performed whenever feasible to alleviate clinical symptoms.

In our study, PRRT was used as first-line therapy in only one patient, and as second- or third-line therapy in all others. Treatment with radiolabeled somatostatin analogues resulted in a favorable response in a substantial proportion of patients, with prolonged survival of 34 and 35 months in patients with stable disease and partial remission, respectively. Only nine patients experienced disease progression following PRRT, and overall survival in these patients was comparable to that observed in patients with stable disease or partial remission. One fatal outcome occurred after the first PRRT cycle following surgery due to postoperative ileus, and no treatment-related adverse effects were observed.

The limitations of this study include the relatively small sample size, as well as the lack of analysis of inflammatory biomarkers during and after PRRT and evaluation of additional risk factors influencing disease outcome, which are addressed in a separate study.

*In conclusion*, PRRT administered according to a three-day nephroprotection protocol represents a reliable and safe treatment option for advanced NEN. It is most commonly applied as a second- or third-line therapy but may also serve as first-line treatment in selected patients with unresectable large tumors. Prolonged progression-free survival and overall survival observed in the majority of patients underline the substantial therapeutic potential of PRRT in advanced NEN.

*The authors declare that they have no conflicts of interest.*

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