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ORIGINAL ARTICLE



Clinical efficacy of first and second series of peptide receptor radionuclide therapy in patients with neuroendocrine neoplasm: a cohort study

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ABSTRACT

Objectives: Peptide receptor radionuclide therapy (PRRT) is an established treatment for metastatic neuroendocrine neoplasms (NEN). However, only limited data exists for the effect of multiple series of PRRT. The aim of this study was to investigate PFS and OS in NEN patients treated with multiple series of PRRT conforming to the ENETS treatment protocol.

Methods: We included all patients with gastrointestinal (GI), pancreatic and bronchopulmonary (BP) NEN treated with PRRT from 2008 to 2018. We used Kaplan-Meier estimation to evaluate PFS and OS with subgroup analysis of primary tumor, Ki67-index, type of radioisotope and number of PRRT series.

Results: 133 patients (female/male 61/72) were included, median age 70 (interquartile range 64–76) years. GI-NEN comprised 62%, pancreatic 23% and BP 11%. Median Ki67-index was 5%. After first PRRT G1- and G2-tumors had PFS of 25 and 22 months, compared to 11 months in G3-NENs ($p < .05$) and PFS was longer in G1/G2 GI-NENs than BP-NEN (30 vs. 12 months, $p < .05$). After retreatment with a second series of PRRT, the overall PFS (G1–G3) was 19 months, with G1- and G2-tumors having the highest PFS of 19 and 22 months, respectively. Overall, the GI and BP tumors had an OS of 54 and 51 months.

Conclusions: PRRT is an effective therapy with long-term PFS and OS, especially in G1 and G2 NENs, and with better prognosis in GI-NEN compared with BP-NENs. OS and PFS was shorter after the second series of PRRT compared with the first, however results were still encouraging.

Abbreviations: NEN: Neuroendocrine neoplasm; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; PRRT: Peptide receptor radionuclide therapy; GI: Gastrointestinal; BP: Bronchopulmonary; GEP: Gastroenteropancreatic; G1/2/3: Grade 1/2/3; ENETS: European Neuroendocrine Tumor Society; RECIST: Response evaluation criteria in solid tumors; CrGFR: Glomerular filtration rate measured by Cr-EDTA plasma clearance; OS: Overall survival; PFS: Progression free survival; 177-Lu: 177-Lutetium; 99-Y: 99-Yttrium; NS: Non-significant

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Introduction

Neuroendocrine neoplasms (NENs) are heterogeneous malignancies arising from the diffuse endocrine system and can arise in almost all organs [1]. NENs are slow-growing and cure can only be achieved by surgery. Unfortunately, most NEN patients are diagnosed with metastatic disease and surgery is therefore not an option [2]. This leads to the need for further options for systemic therapies [3]. Patients with inoperable and metastasized NENs usually receive treatment with somatostatin analogues (SSAs) [4] due to NENs overexpression of somatostatin receptors [5]. Other treatment options include targeted therapy (everolimus [6], sunitinib [7]) or chemotherapy (STZ-5FU [8] and capecitabine/temozolomide [9]).

The overexpression of somatostatin receptors on the cell surface of NENs is also utilized in peptide receptor radionuclide therapy (PRRT) [10]. PRRT is an established treatment

for metastatic neuroendocrine tumors that improves both progression free survival (PFS) and overall-survival (OS) [11–14]. The NETTER-1 study was the first randomized prospective phase III trial comparing ¹⁷⁷Lu-DOTATATE with high dose octreotide in patients with advanced midgut NET. The study showed superior outcome in the PRRT treated group in terms of longer PFS, (28.4 vs. 8.4 months) [15]. A recent retrospective North American cohort study had similar results with a median PFS of 23.9 months and an OS from the first PRRT of 40 months [16].

The outcome of PRRT varies widely depending on tumor type, tumor biology and treatment regimen. Studies are heterogeneous and only few studies have investigated the effect in NEN patients after multiple PRRT series. The Rotterdam group investigated 168 patients who received a second PRRT series and a small group of 13 patients received a third series. They found a median PFS of 14.6 months following the second treatment series and 14.2 months after

the third PRRT series [17]. This need validation, as evidence concerning the cumulative effect in several series of PRRT treatment is scarce.

The aim of this study was to evaluate the PRRT treatment response in a large Danish cohort of patients with NENs following multiple series of PRRT. Patients were evaluated according to primary tumor, tumor grade and treatment type.

Methods

Study design and study population

This was a single-center, cohort study conducted at Aarhus University Hospital, ENETS Centre of Excellence. We included all patients with NENs gastrointestinal (GI), pancreatic and bronchopulmonary (BP) neuroendocrine neoplasms undergoing PRRT according to the ENETS treatment protocol [18] between 2008 and 2018. The majority of PRRT treatments were performed at the Aarhus University Hospital. However, prior to the introduction of PRRT at Aarhus University Hospital in 2008, 15 patients received their first PRRT series in Basel, Switzerland as previously reported [19]. This study included patients with gastrointestinal (GI), pancreatic and bronchopulmonary (BP) NENs, who had completed at least one series of PRRT between 2008 and 2018.

Data was collected from electronic patient files documenting each patient's course of treatment. We extracted data on the origin of primary tumors, proliferation index (Ki67-index), previous therapies, dose and number of PRRT series, along with bone marrow and kidney function (including blood samples and ^{51}Cr -EDTA-plasma clearance) [20].

The follow-up program was identical for the first and the second series of PRRT and comprised a 3-phase CT-scan performed three months after the last PRRT (and subsequently continued with an interval of three months). All scans were discussed at a multidisciplinary team (MDT) conference. The CT was combined with a Ga-68-DOTATOC PET at 6 and 12 months after the last PRRT. Status of the disease (regression, progression or stable) was based on the clinical decision at the MDT-conference. Follow-up imaging and subsequent MDT-conferences were performed at intervals of 6 months after the first rest aging. Status at the last follow-up visit was recorded. If the patients had clinical signs of progression or deterioration extra CT scans were performed.

Treatment

Prior to PRRT, all patients had undergone somatostatin receptor imaging by somatostatin receptor scintigraphy or Ga-68-DOTATOC PET/CT to assure overexpression of somatostatin receptors on tumor cells, with significant uptake than in normal liver tissue. All PRRT treatment decisions were based on a *clinical* decision at the MDT and included radiological progression in all cases.

The initial treatment regimen was typically planned for two or four treatments with PRRT at an interval of 8–12 weeks. This is referred to as one series of PRRT. Routine

blood tests including full blood count, renal and liver function were performed and registered at week 2 and 4 following completion of each treatment series and in between series.

The treatment regimens have changed over time. From 2008 to 2015 the standard regimen was treatment with ^{90}Y -DOTATOC, and we adopted the treatment regimens from Basel [21]. From 2015 the standard regimen was treatment with ^{177}Lu -DOTA-peptide (both in house produced ^{177}Lu -DOTATOC and ^{177}Lu -DOTATE (Lutathera) acquired ready for use) performed according to the EANM guidelines [18]. Combination treatment was used from 2015 in patients with G3-tumors and/or bulky tumors. The standard dose of ^{177}Lu -DOTA-peptide was 7.4 GBq. From 2008 to 2012 the standard dose of ^{90}Y -DOTATOC was 3.7 GBq/m² body surface (a maximum doses of 7.4 GBq/injection), distributed over two treatments with an interval of 8–10 weeks. In 2013, this was changed to four treatments (with an interval of 8–10 weeks) with a standard dose at 1.85 GBq/m² body surface (maximum 3.7 GBq/injection) [12,22]. The decision to re-treat patients with a second or third cycle was primarily based on a combination of the duration of response, toxicity and degree of uptake on SSTR-PET. Patients who developed progression within 12 months were excluded from retreatment.

The use of long-acting SSA was always discontinued 6 weeks before each PRRT treatment while symptomatic patients were allowed short-acting SSA up to 24 h before PRRT. If patients suffered from carcinoid syndrome, treatment with SSA was also administered between the cycles. Treatment was resumed after the last PRRT treatment in each cycle.

Kidney protection was planned according to baseline estimated glomerular filtration rate (eGFR) and ^{51}Cr -EDTA-plasma clearance (Cr-GFR). To reduce the radiation dose to the kidneys and thereby reducing the nephrotoxic effects of the treatment, amino acid solutions were administered before, and continued after injection to inhibit tubular reabsorption. From 2008 to 2015 all patients received nephroprotection with a commercial mixture (Vamin-18, Fresenius Kabi AG, Bad Homburg, Germany). The mixture contains a combination of various amino acids, the most abundant being L-alanine (16.0 g/1000 ml), L-arginine (11.3 g/1000 ml) and L-lysine (9.0 g/1000 ml). From 2015 all patients received a solution containing arginine and lysine Rolleman-solution [23] (1000 ml of 0.9% NaCl solution containing 2.5% arginine and 2.5% lysine), according to the so-called Rotterdam protocol [18]. In patients with $\text{eGFR} > 50 \text{ ml/min}$ a solution containing a 50 g cocktail of lysine and arginine (25 g of lysine and 25 g of arginine) was diluted in 2 liters of normal saline and infused over 4 h, starting 30–60 min (min) before PRRT. If the kidney function was decreased ($\text{eGFR} < 50 \text{ ml/min}$ and $> 40 \text{ ml/min}$) 2 liters of lysine (2.5%) and arginine (2.5%) mixture with 1 liter of saline was infused over 12 h, starting 60 min before PRRT and continuing over 12 h with 170 ml/hour. An extra bolus of 1/2 liter of the mixture 24 h after PRRT. In patients with $\text{eGFR} 30\text{--}40 \text{ ml/min}$ 3 liters of lysine (2.5%) and arginine (2.5%) mixture with 1–2 liter of saline, was infused over 24 h, starting 60 min before PRRT and

continuing over 24 h with 125 ml. per hour. An extra bolus of 1/2 liter of the mixture is given 48 h after PRRT [20,24].

Statistical analyses

Patient data were captured and managed in an electronic REDCap database hosted at Aarhus University [25]. The baseline characteristics of the study population were stratified with regard to primary tumor site. Continuous data are presented as medians with interquartile ranges (IQR) 25th–75th percentiles, and categorical data as proportions with percentages. The PFS was calculated as months from the date of the first treatment of PRRT to the date of progression or death of any course. OS was calculated from the first day of treatment until the day of death of any course. Kaplan–Meier estimates were used to determine PFS and OS, by assessing the time between the date of the first PRRT to date of progression or death of any cause (or to the date of censoring for patients known to be alive). Subgroup analyses were performed according to the primary tumor site, Ki67-index, previous surgery, type of PRRT (isotope) and number of PRRT series. Patients were censored at the last follow-up if they were without progression and at start of analysis (27th august 2019) if they were still alive. The subgroups were compared using an uni-stratified log-rank test. A value of $p < .05$ was considered statistically significant. Hazard ratios were estimated by uni-variate proportional hazards Cox-model. Statistical software (Prism, version 8.0) was used to analyze the data.

Ethical statement

The study was approved by the local ethics committee, The Central Denmark Region Committees on Health Research Ethics (656236).

Results

Patients

From 2008–2018 a total of 150 patients, 61 (46%) female and 72 (54%) male, were treated at the department of Hepatology and Gastroenterology Aarhus (15 were treated in Basel before treatment in Aarhus [19]). Their median age was 70 years (IQR64–76). Ten patients (6.6%) diagnosed with either paragangliomas or meningioma were excluded. Seven patients (4.6%) were excluded as they had either not completed a full series of PRRT or were awaiting follow-up evaluation at the time of analysis. In total, we included 133 patients for the final analysis. However, six patients did not have a follow-up visit before time of death.

Information on the Ki-67 index of the primary tumor or metastases was available for 123 patients (92%). The majority of the patients (63%) had G2 NEN with median Ki-67 index 5% (range 3–15%). Twenty-four patients (20%) had G1 tumors (defined as Ki-67 index $\leq 2\%$) and 21 (17%) had a G3 tumor (Ki-67 index $> 20\%$). Baseline characteristics including

location of primary tumor, disease stage and previous medical treatment and interventions are shown in Table 1.

Peptide receptor radionuclide therapy

In the first series, 66 (50%) patients were treated with ⁹⁰Y-DOTATOC, 60 (45%) were treated with ¹⁷⁷Lu-DOTA-peptide and 7 (5%) with the combination of the two. A second PRRT series was given to 36 (27%). Among these patients, 8 (23%) were treated with ⁹⁰Y-DOTATOC, 25 (69%) with ¹⁷⁷Lu-DOTA-peptide and 3 (8%) with a combination. A third series of PRRT was offered to 8 patients (6%), where 2 (25%) were treated with ⁹⁰Y-DOTATOC and 6 (75%) with ¹⁷⁷Lu-DOTA-peptide (Table 2). In all patients (with completion of at least two series of PRRT) the median time from the last treatment in the first series to the first treatment in the second series was 21 months. The time for the GI-tumors ($n=21$) was 20 months, while it was 30 months for pancreatic tumors ($n=8$) and 29 months for pulmonary tumors ($n=4$) (NS). The time for the G1 tumors ($n=8$) was 19 months, while it was 33 months for G2 tumors ($n=22$) and 21 months for G3 tumors ($n=3$) (NS).

Progression free survival

The final number enrolled into the survival analysis was 133 patients. Six (5%) patients died before follow-up and 7 patients (5%) did not have a follow up visit after their second or third series of PRRT.

First series

A CT was performed 3 months after the last PRRT cycle in a treatment series. In all patients with G1 and G2 tumors, regardless of primary tumor and the radiopharmaceutical administered, we observed progression in 83 patients (62%) and disease regression in 50 patients (38%). The overall median PFS was 25 (11–41) months. The PFS according to primary tumor site (GI, pancreatic and BP) in G1 and G2 NEN patients is presented in Figure 1(A). PFS was 30 (12–41), 19 (9–53) and 12 (9–22) months, respectively, and with a significant difference between GI and BP NENs (p -value $< .05$), and with an associated odds ratio of 0.33 (0.13–0.84). PFS was compared according to tumor grade as shown in Figure 1(B). The G1- and G2-tumors had a PFS of 25 (11–36) and 22 (10–41) months, while the G3-tumor had a PFS of 11 (5–29) months (NS).

There was no significant difference in PFS between patients treated with ¹⁷⁷Lu or ⁹⁰Y in the first series of PRRT with median PFS of 28 (10–35) months and 22 (10–40) months, respectively (NS).

Second series

After the second series of PRRT, progression was observed in 23 patients (64%) with a median PFS of 19 (10–32) months,

Table 1. Patient characteristics at baseline ($n = 133$).

	All sites ($n = 133$)	Pancreas ($n = 31$)	GI ($n = 82$)	Pulmonary ($n = 14$)	Other sites ($n = 6$)
Primary tumor					
Age, median (IQR)	70 (64–76)	67 (59–75)	71 (66–76)	70 (63–75)	66 (62–71)
Gender, n (%)					
Female	61 (46)	13 (42)	41 (50)	4 (29)	3 (50)
Male	72 (54)	18 (58)	41 (50)	10 (71)	3 (50)
Organ metastases, n (%)					
Local	89 (67)	16 (52)	61 (74)	9 (64)	3 (40)
Liver	115 (87)	28 (90)	72 (90)	11 (79)	4 (67)
Bone	40 (30)	8 (26)	18 (22)	12 (86)	2 (33)
Other	14 (11)	3 (10)	8 (10)	1 (7)	2 (33)
Ki67-index, median (IQR)	5 (3–15)	10 (5–25)	5 (2–10)	10 (5–15)	40 (23–40)
≤ 2	24 (20)	1 (3)	23 (28)	0	0
$> 2 \leq 20$	78 (63)	21 (68)	45 (55)	11 (85)	1 (17)
> 20	21 (17)	9 (29)	7 (9)	2 (15)	3 (50)
Previous treatment, n (%)					
Surgery	52 (39)	5 (16)	43 (52)	6 (43)	1 (17)
Somatostatin analogues	113 (85)	21 (68)	78 (97)	10 (77)	4 (67)
Interferones	42 (37)	7 (23)	27 (31)	6 (46)	2 (33)
Chemotherapy	67 (51)	28 (90)	20 (24)	8 (62)	5 (83)
RFA/TAE	11 (8)	3 (10)	7 (9)	1 (8)	0 (0)

IQR: interquartile range; GI: gastrointestinal (includes small intestines and colon); RFA: radiofrequency ablation; TAE: transarterial embolization; Ki-67 index was available for 123 (92%); Chemotherapy includes Sunitinib, STZ/5FU, Temozolomid/Capecitabin, Carboplatin/Etoposid.

Table 2. Peptide receptor radionuclide therapy.

⁹⁰ Y-DOTATOC						¹⁷⁷ Lu-DOTA-peptid					
Administered activity (GBq)		No. of cycles				Administered activity (GBq)		No. of cycles			
		I	II	III	IV			I	II	III	IV
1st series	4.47	3 (5)	33 (50)	4 (6)	26 (39)	7.40	4 (7)	6 (10)	4 (7)	46 (76)	
2nd series	6.70	4 (50)	1 (12)	0 (0)	3 (38)	7.40	2 (8)	6 (24)	0 (0)	17 (68)	
3rd series	5.0	1 (50)	1 (50)	0 (0)	0 (0)	7.40	1 (17)	1 (17)	1 (17)	3 (50)	

Number of patients who received one, two, three or four cycles in the 1st, 2nd or 3rd series of PRRT.

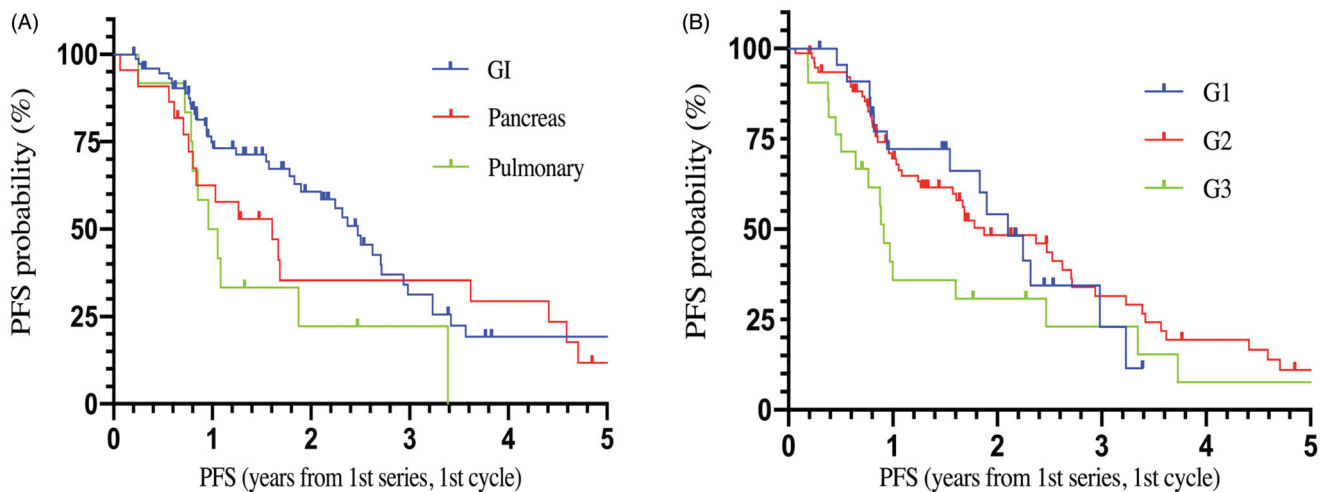


Figure 1. Progression free survival after first series of PRRT. (A) PFS of all G1 and G2 tumors stratified according to primary tumor after the 1st series of PRRT. There was no significant difference between GI NET ($n = 75$) and pancreatic NET ($n = 22$), nor between BP NET ($n = 12$) and pancreatic NET. There was a significant difference GI NET and BP NET (p -value < 0.05). (B) PFS stratified by tumor grade after the 1st series of PRRT. G1 ($n = 23$), G2 ($n = 77$) and G3 ($n = 21$). (NS).

including all patients with G1 and G2 tumors. Only 3 patients with G3 tumors received a second series of PRRT. When G1- and G2-tumors were divided according to primary tumor we found a higher median PFS for GI-NET of 19 (9–26) months, compared to 33 (11–36) months for pancreas and 26 (4–19) months for BP-NET (Figure 2(A)) ($p < .05$). G1- and G2-tumors

showed a PFS of 19 (6-not reached) and 22 (10–33) months, respectively. The G3 tumors had a PFS of 4 (1–16) months (Figure 2(B)) (NS).

Patients treated with ^{177}Lu in the second series of PRRT had a PFS of 16 (9–33) months, while patients treated with ^{90}Y had a PFS of 22 (9–29) months (NS).

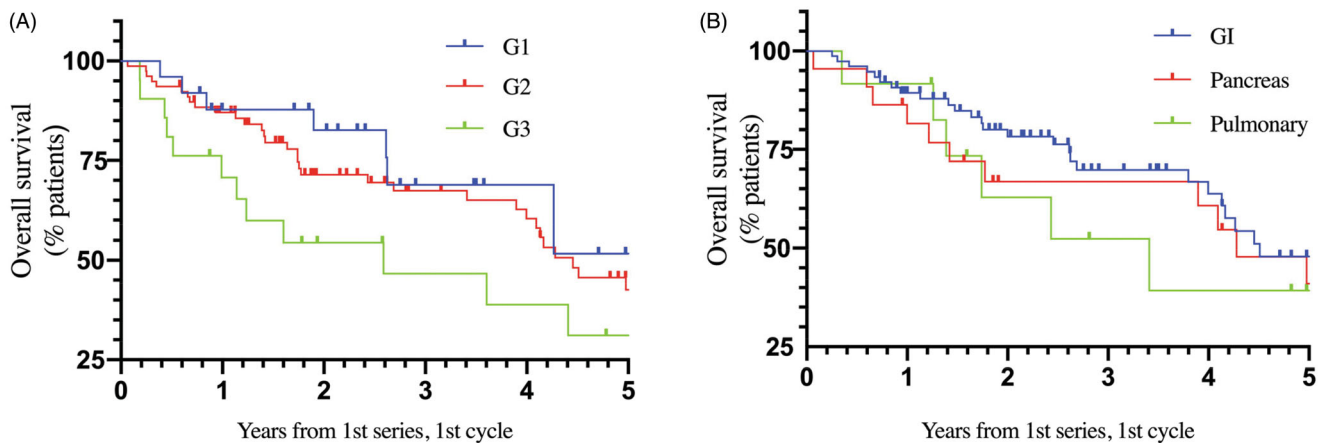


Figure 2. Progression free survival after second series of PRRT. (A) PFS of all G1 and G2 tumors stratified according to primary tumor after the 2nd series PRRT, 1st cycle. There was no significant difference between GI NET ($n = 19$), pancreatic NET ($n = 3$) and BP NET ($n = 5$). (B) PFS stratified by tumor grade after the 1st series of the 2nd PRRT series, 1st cycle. No significant difference between G1 ($n = 7$) and G2 ($n = 20$), nor between G1 and G3 ($n = 3$). There was a significant difference between G1 and G3 (p -value = .02).

PFS by number of PRRT series

The median PFS after the first ($n = 133$) and second series ($n = 32$), was 21 (10–41) vs. 17 (10–27) months, while PFS was 12 (8–15) months after the third series ($n = 8$) with a significant difference in PFS after the first and third series ($p < .05$).

PFS by gender and liver tumor burden

The median PFS in females ($n = 61$) was 20 months (29–75 percentile not reached) compared to 21 (16–79) months in males ($n = 72$) (NS). The median PFS in patients with liver metastasis ($n = 115$) was 20 (10–36) and 12 (10–, 75 percentile not reached) in patients with no liver metastasis (NS).

Overall survival

65 patients (49%) died during follow up. The median OS for the whole cohort was 51 (21–119) months. The median OS for the G1-tumors was not reached whereas the G2 and G3 tumors had an OS of 53 months (21–128) and 31 (10–87) months, respectively (Figure 3(A)) (NS). In addition, we divided all G1 and G2 tumors into three subgroups according to primary tumor site. The GI-tumors had an OS of 54 (31–123) months, while pancreatic- and BP tumors had an OS of 51 (15–72) and 40 (10–75 percentile not reached) months, respectively (Figure 3(B)) (NS).

There was no significant difference between in OS between patients with liver metastasis ($n = 115$) and patients without liver metastasis ($n = 18$) who had a median OS of 54 (22–128) and 53 (11–75 percentile not reached) months, respectively (NS). Further, there was no significant difference in OS between female and males with median OS of 85 (29–75 percentile not reached) and 50 (16–118) months, respectively (NS). An associated Hazard ratio of 0.63 (95% CI 0.39 to 1.04) was found. 26 female and 41 males died during the follow-up period.

Bone marrow- and kidney function

Hemoglobin (Hgb), leukocytes and platelets were used to evaluate the side effects of PRRT on bone marrow function, while ^{51}Cr -EDTA-plasma clearance measurements were used to assess kidney function. Cr-51-GFR plasma clearance was measured before, 3, 6 and 12 months after treatment with ^{177}Lu -DOTA-peptide, and with ^{90}Y -DOTATOC it was measured before, 3, 6, 12 and occasionally 18 and 24 months after PRRT. In between treatments kidney function was monitored with estimated Glomerular filtration rate also called estimated GFR (eGFR). Within our institution the formula to estimate the eGFR is the Modification of Diet in Renal Disease (MDRD) formula [20].

Baseline laboratory assessments were compared with data obtained at the end of treatment (Table 3). We found that in those patients treated with ^{90}Y , the Cr-GFR was reduced by an average of 4%, 7% and 12%, when comparing Cr-GFR before and after first, second and third series of PRRT. In patients treated with ^{177}Lu the Cr-GFR was reduced by 3% and 7% after first and second series, whereas an increase of 3% was observed after the third series. In patients treated with the combination, we found a decrease in Cr-GFR of 9% and 4% after first and second series of PRRT.

Common Toxicity Criteria Scale version 3.0 were used for evaluation [26] and adverse events were accounted severe according to grades III and IV. We found temporary grade III and IV anemia in 4% (3 cases of grade III: Hgb 4.0 to <4.9 mmol/l; 2 case of grade IV: Hgb <4.0 mmol/l). Three patients treated with ^{177}Lu and 3 patients treated with ^{90}Y (Table 4). Leucopenia grade III was found in one patient (total white blood cells ≥ 1.0 to $<2.0 \times 10^9/\text{l}$), treated with ^{177}Lu . No temporary grade III or IV thrombocytopenia was observed.

Due to the retrospective nature of the evaluation, valid numbers on acute side effects could not be provided.

Discussion

In this large cohort study, we confirm an excellent median progression free and overall survival following the first series

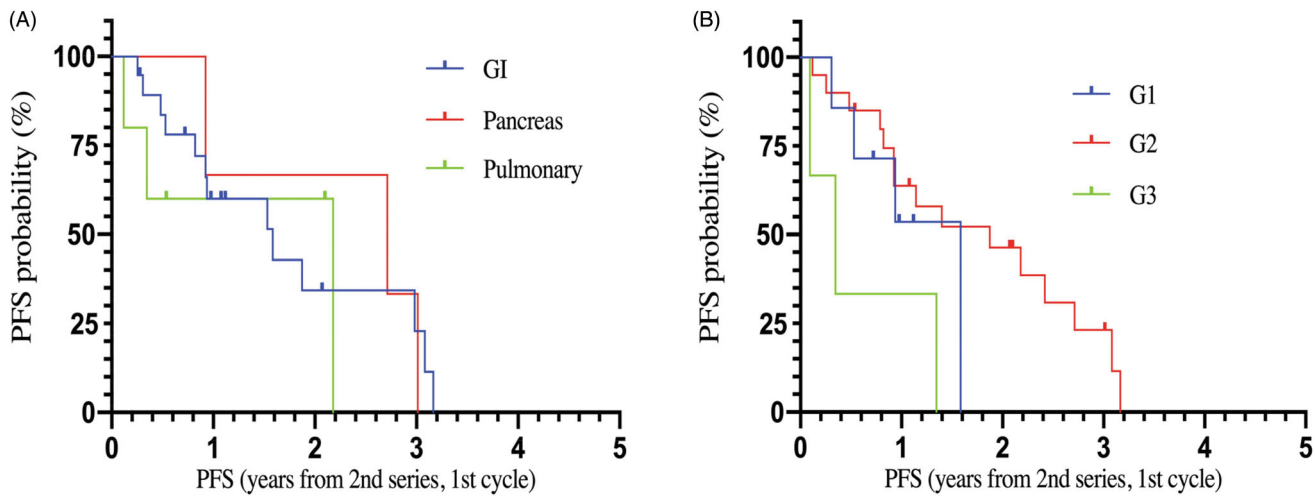


Figure 3. Overall survival. (A) Comparison of OS by tumor grade. There was no significant difference between G1 ($n=24$), G2 ($n=78$) and G3 ($n=21$). (B) Comparison of OS according to primary tumor. GI NET ($n=82$), pancreatic NET ($n=31$) and pulmonary NET ($n=14$). (G3 tumors were excluded). There was no significant difference.

Table 3. The decrease in bone marrow and kidney function by type of PRRT treatment and no. of series.

Type of PRRT	1st series of PRRT		2nd series of PRRT		3rd series of PRRT	
	From baseline to last cycle		From 1st cycle to last cycle		From 1st cycle to last cycle	
	Platelets ^a	Cr-GFR ^b	Platelets	Cr-GFR	Platelets	Cr-GFR
All	-66 (29%)	-6 (8%)	+28 (15%)	-4 (7%)	+10 (5%)	-5 (7%)
⁹⁰ Y	-88 (36%)	-4 (5%)	+31 (17%)	-7 (9%)	+56 (27%)	-12 (16%)
¹⁷⁷ Lu	-63 (-29%)	-3 (9%)	-37 (16%)	-7 (11%)	-12 (7%)	+3 (5%)
Combination	-29 (13%)	-9 (10%)	-64 (31%)	-4 (6%)		

^aUnit: $\times 10^9/l$. Information about platelet count was registered 4 weeks after first cycle and 4 weeks after the last cycle in both series of PRRT. At baseline the platelets were registered for 131 patients (98%) and in 78 (59%) after the last cycle in the 1st series of PRRT. 23 (66%) and 15 patients (43%) were registered after the 1st and last cycle in the 2nd series of PRRT. 5 (63%) and 2 patients (25%) were registered after the 1st and last treatment of the 3rd series PRRT.

^bUnit: ml/min. Cr-GFR was registered before 1st cycle and 4 weeks after the last cycle in each series of PRRT. Cr-GFR was registered in 125 patients (94%) at baseline and in 100 (75%) after the last cycle in the first series of PRRT. 36 (100%) and 25 patients (69%) were registered after the 1st and last cycle of the 2nd PRRT. 8 (100%) and 6 patients (75%) were registered after the 1st and last cycle of 3rd series of PRRT.

Table 4. Anemia – common toxicity criteria scale.

Grade	1st series			2nd series			3rd series		
	⁹⁰ Y	¹⁷⁷ Lu	Combination	⁹⁰ Y	¹⁷⁷ Lu	Combination	⁹⁰ Y	¹⁷⁷ Lu	Combination
III	0	2 (3%)	0	0	0	0	0	0	
IV	1 (1.5%)	1 (2%)	0	0	0	0	1 (50%)	0	

The hemoglobin was registered in 78 (59%) patients after the first series, in 15 (43%) patients after the second series and in 2 (25%) patients after the third series of PRRT.

of PRRT in patients with GEP (gastroenteropancreatic) and BP NEN. In addition, we also provide data to support the use of more PRRT cycles in NET patients progressing after the first series of PRRT treatment.

Our results are comparable with the randomized NETTER-1 study, which only included well differentiated, metastatic GEP-NETs treated with ¹⁷⁷Lu-DOTATATE [15]. They reported a PFS of 28 months compared to our 25 months; however, we also included BP-NETs, who have a shorter PFS. Results also corresponds with the data from another Danish cohort of G1- and G2-GEP NET patients treated in Basel, reporting a PFS of 29 months [19]. Recently, Sharma et al. reported outcomes in a North American cohort with metastatic well-differentiated GEP NETs with a PFS of 24 months. In their cohort both the PFS and the OS was higher in

patients with pancreatic NETs compared to GI-NETs [16]. This was also the case in a retrospective study of pancreatic NET G1/2 tumors with a PFS of 34 months and an OS of 53 months [27]. Both these studies are in contrast to our findings where both the PFS and the OS was higher in patients with GI-tumors. In the present study, Ki67-index was higher in the pancreas group compared to the GI group. A retrospective study by Ezzidin et al. showed that even the distinction between G1 and low-range G2-tumors was significant for the outcome [28]. Given the nature of this retrospective series, care must be taken when interpreting the results, but difference in tumor grade may contribute to the discrepancy. In a recent review, Bodei et al. described interesting pathobiological features, pathways, and candidate genes for radiation sensitivity. In contrast to GI-tumors,

several recurrent mutations were recognized in pancreatic NET, which seem to be promising and holds promise for predicting treatment response in the future [29]. However, we do not have such data which may have added to the understanding to the difference in treatment response between the groups. In accordance with previous studies, we also observed a significant difference between the PFS of GI and BP NETs [10,11]. A recent review summarized several results from previous studies where PFS varied from 17 to 29 months and median OS from 22 to 37 months with differences according to primary tumor and Ki-index [30]. Overall, the PRRT results seem to be rather consistent across the literature.

The median OS in our cohort across all groups was 51 months. There was no significant difference between the OS across the three subgroups, but a strong trend indicated a better survival in G1 and G2 tumors compared with the G3 tumors. The GI-NETs had an OS of 54 months compared to 51 months for pancreatic and 40 months for BP tumors. These results seem to be slightly better than the ones demonstrated by Sharma et al. with an OS of 40 months in their GEP NET G1/2 cohort [16]. The median OS was 35 months longer in females than in males (50 versus 85 months), and although this was not significant, the finding is supported by an associated Hazard ratio for woman of 0.63 (95% CI 0.39–1.04). These findings are in accordance with the NETTER-1 study also demonstrating a lower HR for death in females and this points towards a sex-based heterogeneity in the response to PRRT.

Only a few studies have included G3 tumors. Ezziddin et al. demonstrated that a Ki-67 index of <20% was predictive of a good response following PRRT while a Ki-67 > 20% was associated with progression within 3 months after PRRT treatment [28]. Aalbersberg et al. also showed that higher Ki-67-values was a negative predictor for both PFS and OS [31]. Further, some studies [32,33] showed an inverse association between tumor grade and tumor uptake on somatostatin receptor imaging. However, patients are scanned to assure overexpression of somatostatin receptors before starting PRRT. That said, our patients with Ki-67 > 20% had a fairly response of PRRT with a PFS of 12 months after the first series of PRRT.

The possible benefit in high-grade GEP NEC (neuroendocrine carcinoma) has until recently been debated. A recent large retrospective cohort study of 149 GEP NEC G3 patients demonstrated promising results [34]. Their results were better in the subgroup with Ki-67 between 21–54% vs Ki-67 ≥ 55% ($p < .001$). Overall, the total cohort had a median PFS of 14 months and OS of 29 months [34]. These results correspond well with our NEC cohort including BP NECs with a PFS of 11 months and an OS of 31 months. Hence, our results support the use of PRRT also in NEC patients.

Interestingly, this study is one of the first to demonstrate a favorable response also after a second series of PRRT with a progression free survival of 19 months across all primary tumors. Recently, results from the large Rotterdam cohort reported a PFS after a second series of PRRT of 15 months, including GEP- and bronchial G1/2 NETs [17]. They also

compared PFS according to primary tumor site (pancreatic ($n = 53$), bronchial ($n = 8$) and midgut ($n = 54$)), where PFS was 14, 8 and 5 months, respectively. Additionally, Vaughan et al reported a median PFS of 18 months [35] after retreatment, whereas Severi et al demonstrated a PFS of 22 months [36] compared to the 12 months in the study by Yordanova [37]. Sabet et al. performed a retrospective study in 33 patients also with encouraging results after a second series of PRRT. Their findings supported that PRRT may be an effective salvage treatment for patients with GEP-NET with a median PFS of 13 months [38]. In contrast, a previous smaller study including 35 mainly GI and BP G2 NET showed the shortest PFS of six months. This is surprising as progression in that study was defined according to RECIST (response evaluation criteria in solid tumors), which would statistically lead to a longer PFS compared to the studies using clinical progression [39]. Our cohort demonstrated an overall PFS of 19 months for GI-NET ($n = 19$), 33 months for pancreatic ($n = 3$) and 26 months for BP ($n = 5$) NET after the second PRRT series. The distribution of tumor grade in our study was similar to the Rotterdam study [17], which explains the similar results. Our analysis is based on few patients and firm conclusions should be drawn with great caution. However, despite the lower PFS compared to the first series, we believe that a second series of PRRT makes sense as it results in a fairly long PFS and OS. The very fast progression in G3 tumors, after a second treatment series, was based on very few patients and no firm conclusions can be drawn.

Only one trial investigated PFS in patients receiving a third series of PRRT and reported a median PFS of 15 months [17]. They included 13 patients with GI- ($n = 4$), pancreatic- ($n = 4$), BP ($n = 2$) and unknown primary ($n = 3$) NETs. These results correspond well with ours with a PFS values of 12 months after a third series of PRRT, including GI ($n = 5$), pancreatic ($n = 1$), BP ($n = 1$) and unknown ($n = 1$) NETs. The median Ki67-index was 5%. Data are limited but we believe that a third series may be favorable in selected patients.

Patients in this study were treated either with ^{177}Lu , ^{90}Y or the combination of the two. Patients treated with ^{177}Lu in the first PRRT series had a median PFS of 28 months, while patients treated with ^{90}Y in the first PRRT series had a PFS of 21 months (NS). The isotope ^{90}Y has larger beta energy and better tissue penetration than ^{177}Lu , and only DOTATOC labeled with ^{90}Y was used for the first seven years at our center. The standard regimes have changed over time and after 2015 we primarily used POTA peptide labeled with ^{177}Lu as our standard treatment, and in 2018 only one patient was treated with ^{90}Y -DOTATOC. However, this study was retrospective and the role of ^{90}Y -DOTATOC has changed, and the ^{90}Y -labelled peptide is by now preferably used in patients with large bulky tumors, which may explain the tendency towards a less favorable result.

Due to the larger beta energy and the better tissue penetration, we would expect that ^{90}Y would have a more significant effect on the kidney and bone marrow function than ^{177}Lu . However, we did not find a significance difference between the side effects of the two treatments. Some missing data might explain the lack of difference between the

two treatments; however, the missing data were evenly distributed among the patients, who received treatment with either ^{90}Y and ^{177}Lu . In accordance with the NETTER-1 trial we observed only mild toxicity in the majority of the patients, and we did not observe any difference in the decrease in kidney function when comparing ^{90}Y and ^{177}Lu .

The major strength of the present study is the high number of well-characterized NEN patients treated at a highly specialized ENETs center of excellence. Follow-up data was almost complete due the standardized treatment course. We included patients starting PRRT in 2008, allowing a long follow-up period, and we used the same Case Report Form (CRF) for all patients.

The study has some limitations. Data from the first treatments completed in Basel and Copenhagen were not as complete as the treatments completed in Aarhus. This, in addition to the patient heterogeneity with regard to primary tumor and Ki-67 index, may have influenced the outcomes. In this cohort, the standard PRRT treatment has changed over the 10-year period since new treatments and new clinical guidelines develop over time. In 2013, the standard PRRT series was changed from two to four ^{90}Y treatments with 8–12 weeks' intervals, and in late 2015 we implemented the use of ^{177}Lu as a first-line treatment. This inconsistency introduces an overtime bias and firm conclusion must be taken with regard to improvements over time. Our response evaluation was based on the clinical decision at a dedicated NET MDT-conference and not RECIST. However, progression was defined as radiological progression and was probably decided at an earlier stage compared with other studies where progression was based on the firm RECIST criteria. Finally, the comparison with other studies should be done with caution due to different treatment protocols, differences in patient populations and disease stages, and with differences in inclusions- and exclusions criteria and follow-up protocols.

Conclusion

In this large cohort study on effects of a first and second series of PRRT treatment at Aarhus University Hospital, we demonstrated an excellent median PFS of 25 months and an overall survival of 51 months after the first series of PRRT in patients with GEP and BP NET. Tumors originating from the GI-tract had a better response than BP tumors, and G1- and G2-tumours responded better than G3. Interestingly, we observed a favorable PFS of 19 months after a second series of PRRT independent on tumor grade. Our findings thus suggest that a second series of PRRT may be favorable in selected patients progressing after their first PRRT series.

Ethical approval

The study was approved by the local ethics committee of Central Region Midt-Jutland and according to national regulations the need for consent was waived (656236).

Author contributions

H. Grønbaek, G. Dam and M. D. Zacho conceived the study. M. D. Zacho extracted the data and performed data analysis in collaboration with G. Dam, H. Grønbaek and S. M. D. Baunwall. P. Iversen, G. E. Villadsen and A. K. Arveschoug evaluated treatment responses. All authors participated in drafting the manuscript and all authors approved the final version.

Disclosure statement

H. Grønbaek has received research grants from Abbvie, Intercept and NOVO Nordisk Foundation, and is on advisory board at Ipsen and speaker for Norgine. The other authors have no conflicts of interest.

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Data availability statement

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

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