RESEARCH

Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study

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Abstract

Peptide receptor radionuclide therapy (PRRT) is an established treatment of metastatic neuroendocrine tumors grade 1–2 (G1–G2). However, its possible benefit in high-grade gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN G3) is largely unknown. We therefore aimed to assess the benefits and side effects of PRRT in patients with GEP NEN G3. We performed a retrospective cohort study at 12 centers to assess the efficacy and toxicity of PRRT in patients with GEP NEN G3. Outcomes were response rate, disease control rate, progression-free survival (PFS), overall survival (OS) and toxicity. We included 149 patients (primary tumor: pancreatic $n = 89$, gastrointestinal $n = 34$, unknown $n = 26$). PRRT was first-line ($n = 30$), second-line ($n = 62$) or later-line treatment ($n = 57$). Of 114 patients evaluated, 1% had complete response, 41% partial response, 38% stable disease and 20% progressive disease. Of 104 patients with documented progressive disease before PRRT, disease control rate was 69%. The total cohort had median PFS of 14 months and OS of 29 months. Ki-67 21–54% ($n = 125$) vs Ki-67 ≥55% ($n = 23$): PFS 16 vs 6 months ($P < 0.001$) and OS 31 vs 9 months ($P < 0.001$). Well ($n = 60$) vs poorly differentiated NEN ($n = 62$): PFS 19 vs 8 months ($P < 0.001$) and OS 44 vs 19 months ($P < 0.001$). Grade 3–4 hematological or renal toxicity occurred in 17% of patients.

Key Words

- neuroendocrine tumors
- neuroendocrine carcinoma
- neuroendocrine neoplasm
- high-grade
- peptide receptor radionuclide therapy
- radiolabeled somatostatin analogues
- ^{177}Lutetium
- ^{90}Yttrium
- progression-free survival
- overall survival

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This large multicenter cohort of patients with GEP NEN G3 treated with PRRT demonstrates promising response rates, disease control rates, PFS and OS as well as toxicity in patients with mainly progressive disease. Based on these results, PRRT may be considered for patients with GEP NEN G3.

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Introduction

Neuroendocrine neoplasms (NENs) are a very heterogeneous entity classified according to primary tumor location, stage, proliferation rate and differentiation. The 2010 World Health Organization (WHO) Classification grades NEN according to the proliferation index Ki-67; ≤2% (Grade 1, G1), 3–20% (G2) and >20% (G3) (Bosman *et al*. 2010). G1–G2 was collectively referred to as neuroendocrine tumors (NET) and G3 as neuroendocrine carcinoma (NEC). The classification is strongly prognostic, but is also used to guide treatment decisions. In 2017, WHO refined the classification of pancreatic NEN; G3 tumors are further classified as well (NET G3) and poorly differentiated (NEC) based on morphology (Kloppel *et al*. 2017), and a similar expansion to gastrointestinal (GI) G3 tumors is anticipated in the next WHO classification. The NET category is now only used for well-differentiated tumors regardless of their proliferation index (G1–G3), whereas the NEC category is used for poorly differentiated high-grade neuroendocrine carcinomas (G3). The terminology of NEN G3 relates to all high-grade (G3, Ki-67 >20%) neuroendocrine malignancies; i.e. both NET G3 and NEC.

Gastroenteropancreatic (GEP) NENs G3 are rare, highly malignant, with poor prognosis and limited therapeutic options (Sorbye *et al*. 2014, Ilett *et al*. 2015, Garcia-Carbonero *et al*. 2016). The majority of patients have metastases at the time of diagnosis and median overall survival (OS) is less than 6 months including all patients (Dasari *et al*. 2018). Platinum-based chemotherapy is the standard treatment in metastatic disease with response rates of 30–35%, progression-free survival (PFS) of 4–5 months and OS 11–14 months (Sorbye *et al*. 2013, Yamaguchi *et al*. 2014, Heetfeld *et al*. 2015, Walter *et al*. 2017).

In metastatic GEP NET G1–G2, peptide receptor radionuclide therapy (PRRT) targeting somatostatin receptors has been used with excellent results for the last two decades in Europe and Israel (Kwekkeboom *et al*. 2008, Bodei *et al*. 2011, Imhof *et al*. 2011, Pfeifer *et al*. 2011, Romer *et al*. 2014). The recent NETTER-1 phase 3 trial of patients with somatostatin receptor imaging (SRI)-positive NET G1/G2 supports this approach (Strosberg *et al*. 2017). In contrast, PRRT has generally not been recommended for GEP NEN G3 based on expectance of low expression of somatostatin receptors and rapid growth behavior. According to guidelines, PRRT can be considered in SRI-positive NET G3, but data are lacking (Garcia-Carbonero *et al*. 2016). PRRT could, however, be a relevant therapeutic option for NEN G3 since SRI positivity has been reported for both NET G3 and NEC (Sorbye *et al*. 2013, Velayoudom-Cephise *et al*. 2013, Heetfeld *et al*. 2015, Raj *et al*. 2017), as well as having expression of somatostatin receptor 2A on immunohistochemistry (Konukiewitz *et al*. 2017).

Randomized large studies to assess the benefit of specific treatments are often not feasible to perform in very rare diseases. Large retrospective datasets may then initially be the only way on which to base treatment decisions. In a large multicenter international cooperation, we therefore collected retrospectively the outcomes after PRRT in patients with GEP NEN G3.

Methods

Patients

At 12 university hospitals, we retrospectively included patients that fulfilled the following criteria: (1) GEP NEN or NEN of unknown primary with dominance of abdominal metastases, (2) Ki-67 >20% and (3) treated with PRRT. Data on demographics, diagnosis, previous treatments, PRRT, outcome and toxicity were registered. SRI (^{68}Ga-somatostatin analogue positron emission tomography (PET)/computer tomography (CT) or ^{111}In-octreotide or ^{99m}Tc-tektrotyd scintigraphy) results were reported as tumor uptake in relation to liver uptake (none, <liver, =liver or >liver) and used as a surrogate for somatostatin receptor density. ^{18}F-flour-deoxy-glucose (FDG) PET/CT results were reported as tumor uptake present or not (positive or negative by qualitative assessment). Histological examination included chromogranin A (CgA) and synaptophysin staining, Ki-67% in hot spots and tumor differentiation (poor, intermediate

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and well). Most of the centers have specific NET pathologists and in cases where differentiation was lacking in the original pathology report, a reclassification was done if sections were available. Plasma values of CgA, lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) were determined shortly before the first PRRT cycle, and regularly afterward during and after the end of PRRT.

Patients were grouped according to Ki-67 index (21–54% and ≥55%) based on the Nordic NEC study and other reports (Sorbye *et al*. 2013, 2018, Garcia-Carbonero *et al*. 2016, Thang *et al*. 2018). Furthermore, patients were grouped by combined Ki-67% and differentiation: Ki-67: 21–54% and well-differentiated tumor (NET G3) vs Ki-67: 21–54% and poorly differentiated tumor (NEC; Ki-67 21–54%) vs Ki-67 ≥55% and poorly differentiated tumors (NEC; Ki-67 ≥55%) (Milione *et al*. 2017).

Ethical committee approval was obtained in accordance with regional guidelines (either approval of the study or exempt of application due to the retrospective design). Regional ethics committees for participating centers are Rigshospitalet (Videnskabsetisk Komité, Region Hovedstaden) and Aarhus University Hospital (Videnskabsetisk Komité, Region Midt), Denmark; University Hospital Bonn (Ethikkommission an der Medizinischen Fakultät der RheinischenFriedrich-Wilhelms-Universität Bonn) and University Hospital Gießen and Marburg (Ethics Committee of the Philipps-University Marburg, Medicine), Germany; Hadassah-Hebrew University Medical Center (Hadassah-Hebrew University Medical Center Institutional Ethical Committee), Israel; European Institute of Oncology (Ethics Committee), Italy; Erasmus Medical Center (Medical Research and Ethics Committee, Rotterdam), The Netherlands; MSWiA Hospital Warsaw (Komisja Etyki i Nadzoru nad Badaniami na Ludziach), Poland; Uppsala University Hospital (Uppsala Regionala Etikprövningnämnden), Sweden; University Hospital Basel (Ethikkommission beider Basel), Switzerland; Churchill Hospital (Oxford Research and Ethics Committee) and Imperial College London (Regional Ethics Committee of Wales), United Kingdom. Patients gave informed consent before receiving PRRT.

Treatment

Patients received PRRT according to local guidelines at their respective institution. In general, treatment was given intravenously and consisted of a radioisotope (^{177}Lutetium, ^{90}Yttrium or ^{111}Indium) conjugated with a somatostatin analogue (octreotide or octreotate). Patients were planned to a series of PRRT, typically consisting of four cycles each and separated by approximately 8 weeks. The intended cumulative activity was calculated by taking renal function and bone marrow irradiation into account. To reduce renal irradiation, patients were pretreated with an intravenous amino-acid solution. Planned PRRT cycles were discontinued in case of progression of disease or adverse effects limiting further cycles.

Outcomes

Response rate (RR) was defined as complete response (CR) or partial response (PR) according to the response evaluation criteria in solid tumors (RECIST 1.1) (Eisenhauer *et al*. 2009). Disease control rate (DCR) was defined as CR or PR in all patients or stable disease (SD) in patients with progressive disease (PD) at the start of PRRT. PFS was time from first cycle of PRRT to disease progression radiologically by RECIST 1.1 or clinically assessed by a physician (i.e. worsening of performance status due to NEN). If no progression was documented, date of death or date of last follow-up if alive was used. OS was time from first cycle of PRRT to death or date of last follow-up if still alive. Toxicity was reported as acute if occurring during PRRT and as long term if occurring after PRRT and within 1 year of PRRT. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v.4, reporting grade 3–4 only.

Statistics

Continuous variables are reported as median and range. By means of Kaplan–Meier estimation, PFS and OS was calculated and reported as median with 95% confidence interval (CI). Log-rank test was used to compare PFS and OS estimates between groups. Cox regression analysis was performed for PFS and OS with covariates: age, gender, performance status (PS), SRI tumor uptake, Ki-67 (dichotomized), primary tumor site, tumor morphology (well vs poorly differentiated, excluding the intermediate group due to few cases), plasma LDH and plasma ALP. Chi-square and Mann–Whitney *U* tests were used to assess baseline variables associated with discontinuation of planned PRRT and PD as best response to PRRT. *P* values <0.05 were considered statistically significant. All analyses were performed using SPSS statistics 25.

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Results

Patients

From August 1999 to May 2017, 149 patients with GEP NEN G3 received PRRT at 12 centers (Table 1). The primary tumor site was predominantly in the pancreas ($n=89$) or unknown ($n=26$). Other sites included the esophagus ($n=2$), stomach ($n=4$), gallbladder/common bile duct ($n=2$), small bowel ($n=18$), colon ($n=3$), rectum ($n=3$) and other abdominal sites ($n=2$), here collectively referred to as GI ($n=34$). All but two patients had metastatic disease. The median Ki-67 was 30%, ranging from 21 to 100%. Ki-67 21–54% was found in the majority of patients ($n=125$) vs ≥55% ($n=23$), missing for one patient. Tumor morphology was equally distributed among poorly ($n=62$) and well differentiated ($n=60$) with only few cases of intermediate differentiation classification ($n=9$). Seventeen of 20 patients (85%) with Ki-67% ≥55% vs 44 of 110 patients (40%) with Ki-67 21–54% had poorly differentiated tumor morphology. All patients with SRI showed tumor uptake, predominantly >liver uptake.

Treatment

At the start of PRRT, 104 patients (70%) had radiologically progressive disease (determined by RECIST in 67 patients), which also was the main indication for PRRT (65%) (Table 2). The median time from diagnosis to first PRRT was 8 months (range 0–174). PRRT was frequently given as second line ($n=62$) or a later line of treatment ($n=57$). Patients received a median of four cycles PRRT (range 1–15) with a median cumulative activity of 18 gigabecquerel (range 4–85). Radioisotopes ^{177}Lutetium and/or ^{90}Yttrium were used for PRRT in all patients other than a single patient who received ^{111}Indium. Concurrent chemotherapy was used in six patients (4%). Overall, 98 patients (66%) completed their planned protocol of PRRT cycles, while 51 patients did not (Table 2). The main reasons for not completing the planned PRRT cycles were progressive disease ($n=19$), clinical deterioration ($n=6$) or toxicity ($n=6$). Pre-treatment variables (Table 1) associated with discontinuation of PPRT were poor tumor differentiation, unresected primary tumor and elevated plasma LDH ($P<0.05$). Data on treatment after PRRT was available for 118 patients (79%). Chemotherapy ($n=65$) and somatostatin analogs (SSA) ($n=67$) were frequently used, while surgery on the primary tumor or metastases ($n=8$), liver embolization ($n=12$) and external radiotherapy ($n=19$) were less frequently used.

Table 1 Baseline characteristics of 149 patients with GEP NEN G3 receiving PRRT.

Characteristics	Value
Age (years)	57 (24–85)
Time since diagnosis (months)	8 (0–174)
Gender	
Male	76 (51)
Female	73 (49)
Performance status	
0	74 (50)
1	41 (28)
2	11 (7)
Missing	23 (15)
Primary tumor site	
Pancreas	89 (60)
Gastrointestinal	34 (23)
Unknown primary	26 (17)
Metastatic disease	147 (99)
Liver metastases	141 (95)
Tumor differentiation	
Well	60 (40)
Intermediate	9 (6)
Poor	62 (42)
Not specified	18 (12)
Percentage Ki-67	30 (21–100)
Ki-67	
21–54%	125 (84)
≥55%	23 (15)
Not specified	1 (1)
Ki-67 and differentiation	
NET G3	58 (39)
NEC; Ki-67 21–54%	44 (30)
NEC; Ki-67 ≥55%	17 (11)
Not specified	30 (20)
CgA staining of tumor	
Strongly positive	90 (60)
Partly positive	19 (13)
Negative	9 (6)
Not specified	31 (21)[a]
Synaptophysin staining of tumor	
Strongly positive	105 (71)
Partly positive	11 (7)
Not specified	33 (22)
SRI available	146 (98)
Uptake	
None	0
<Liver	5 (3)
=Liver	10 (7)
>Liver	131 (88)
^{18}F-FDG PET/CT available	39 (26)
Tumor positive (out of available ^{18}F-FDG PET/CT)	34 (87)
Plasma-CgA	
Normal	15 (10)
Elevated	83 (56)
Missing	51 (34)
Plasma-LDH	
Normal	76 (51)
Elevated	35 (24)
Missing	38 (26)

(Continued)

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Table 1 Continued.

Characteristics	Value
Plasma-ALP	
Normal	54 (36)
Elevated	67 (45)
Missing	28 (19)
Number of prior lines of medical treatment	
0	30 (20)
1	62 (42)
2	31 (21)
>2	26 (18)
Prior treatment	
Primary tumor resected	58 (39)
Somatostatin analog	74 (50)[b]
Chemotherapy/targeted therapy	
In total	88 (59)
Cisplatin	31 (21)
Carboplatin	26 (17)
Etoposide	46 (31)
Capecitabine/5-fluorouracil	38 (26)
Temozolomide	19 (13)
Streptozotocin	13 (9)
Everolimus	9 (6)
Doxorubicin	5 (3)
Sunitinib	4 (3)
Oxaliplatin	4 (3)
Interferon	2 (1)

Age, time from diagnosis and Ki-67 are given as median with range; other variables are number with percentages.
[a]In 29 patients, CgA and synaptophysin staining results were not available; hereof 28 patients had SRI available that showed tumor uptake; [b]missing values for seven patients.
^{18}F-FDG PET/CT, Flour-Deoxy-Glucose positron emission tomography/computer tomography; ALP, alkaline phosphatase; CgA, chromogranin A; GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; LDH, lactate dehydrogenase; PRRT, peptide receptor radionuclide therapy; SRI, somatostatin receptor imaging.

Response and survival analysis

Of 114 patients evaluable by RECIST, 1 (1%) had CR, 47 (41%) PR, 43 (38%) SD and 23 (20%) PD. An example of a PR is shown in Fig. 1. Disease control was seen in 79 patients (69%) responding to PRRT. RR did not differ among subgroups, including differentiation (42 vs 43% for well and poorly differentiated, respectively) and Ki-67 index (42% vs 43% for Ki-67 21–54% and Ki-67 ≥55%, respectively) (Table 3). RR was similar for patients treated with ^{177}Lu (40 of 86 patients) and ^{90}Y (5 of 16 patients) PRRT. Furthermore, we observed similar RR from the 12 centers (data not shown). Pre-treatment variables (Table 1) associated with PD were poor tumor differentiation, Ki-67 ≥55%, and elevated plasma LDH ($P<0.05$). Median follow-up was 23 months (range 0–210), and during follow-up 107 patients died. The cause of death was NEN in 91 of 94 cases with available data. The median PFS was 14 months (95% CI 10.4–17.6) and median OS was

Table 2 Treatment details and toxicity of PRRT for 149 patients with GEP NEN G3.

	Value
Radiologically progressive disease at start of PRRT	
Yes	104 (70)
No	35 (24)
Unknown	10 (7)
Indication for PRRT	
Progression of disease	97 (65)
First line	30 (20)
Side effects (not further specified) to other therapies	6 (4)
Other	16 (11)
Radioisotope	
^{177}Lutetium	101 (68)
^{90}Yttrium	34 (23)
^{177}Lutetium + ^{90}Yttrium	12 (8)
^{111}Indium	1 (1)
Not specified	1 (1)
Cumulative activity (gigabecquerel)	18 (4–85)
Number of PRRT cycles	4 (1–15)
Fulfilled planned number of cycles	98 (66)
Discontinuation of PRRT	
Disease progression	19 (13)
Clinical deterioration	6 (4)
Hematological side effects	5 (3)
Renal side effects	1 (1)
Lack of compliance	1 (1)
Other	17 (11)
Not specified	2 (1)
Performance status after treatment	
0	74 (50)
1	34 (23)
2	11 (7)
3	5 (3)
Not specified	25 (17)
Absence of acute toxicity (grade 3–4)	121 (81)
Patients with acute toxicity[a]	19 (13)
Hematological, grade 3/grade 4,	8/1
Renal	2/1
Diarrhea	0/2
Nausea	0/2
Other, not specified	14/1
Unknown	9 (6)
Absence of long-term toxicity (grade 3–4)	101 (68)
Patients with long-term toxicity[a]	19 (13)
Hematological, grade 3/grade 4,	13/2
Renal	3/0
Other, not specified	3/3
Unknown	29 (20)

Cumulative activity and number of PRRT cycles are given as median with range; other variables are number with percentage.
[a]More than one toxicity may be present in a patient.
GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; PRRT, peptide receptor radionuclide therapy.

29 months (95% CI 23.3–34.7) for all patients. Median PFS and OS were significantly longer for patients with a Ki-67 21–54% ($P<0.001$), well-differentiated tumor ($P<0.001$), PS <2 ($P<0.001$), normal plasma levels of LDH ($P<0.001$) and ALP ($P<0.001$) (Figs 2 and 3). PFS and OS

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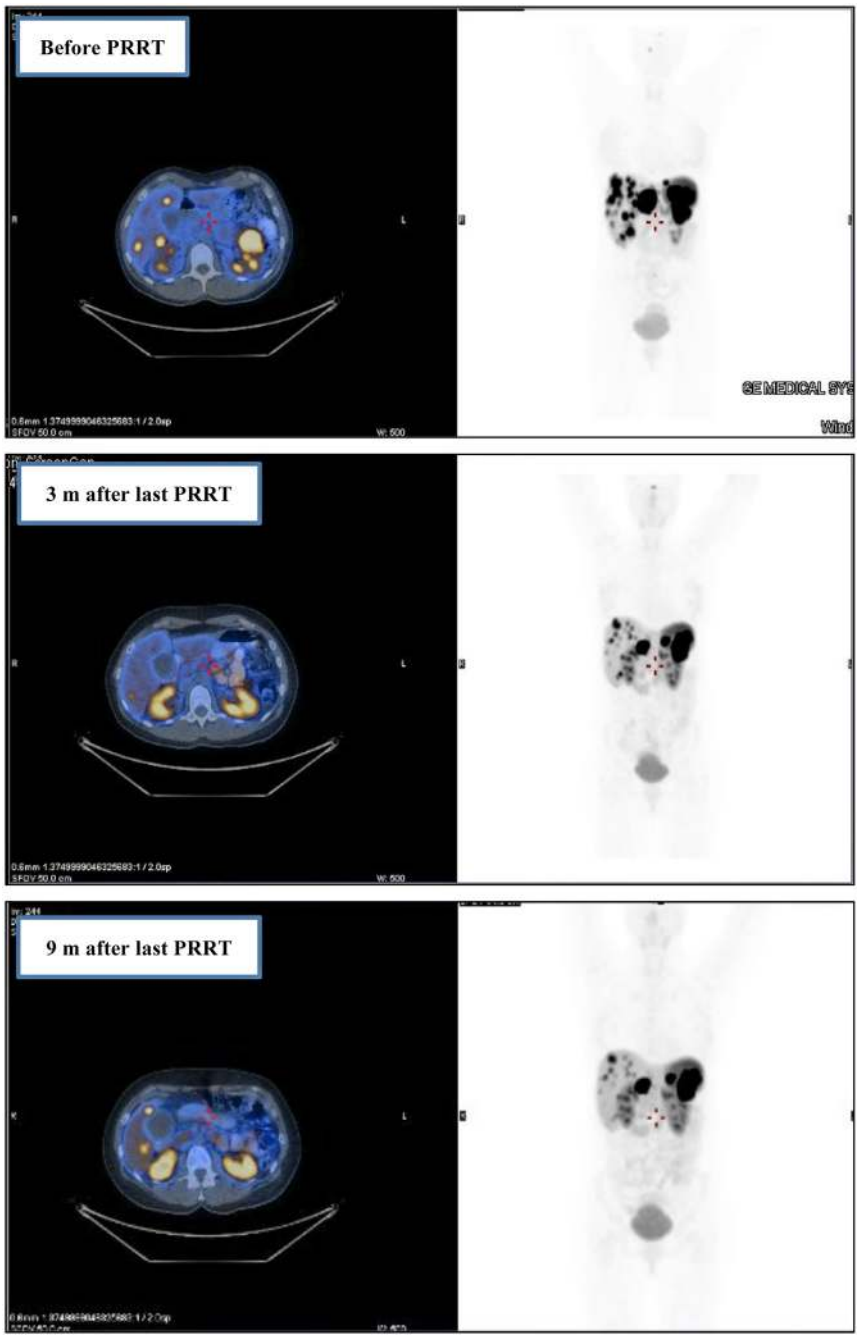

Figure 1
An example of PRRT in GEP NEN G3. Left-hand side: fused positron emission tomography (PET) and computer tomography (CT), transverse plane at kidney level. Right-hand side: whole-body maximum intensity projection, PET. A 47-year-old female with high-grade pancreatic neuroendocrine neoplasm (Ki67 of 70%), metastatic to the liver. Received three cycles of peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE. Follow-up with a durable partial response. PRRT, petide receptor radionuclide therapy; m, months. A full colour version of this figure is available at https://doi.org/10.1530/ERC-18-0424.

were independent of the amount of SRI tumor uptake, primary tumor site and line of treatment. In univariate analyses of PFS and OS, Ki-67 index, differentiation, PS as well as plasma LDH and ALP were statistically significant predictors (Table 4). In multivariate analysis (n=75), PS, plasma LDH and ALP were statistically significant predictors for PFS and OS, and age was significant for PFS and differentiation for OS (Table 5). Excluding plasma LDH and ALP from the multivariate analysis resulted in 106 patients in the model; differentiation and PS were statistically significant predictors for PFS and OS (data not shown).

Toxicity

Acute grade 3–4 toxicity occurred in 19 patients (13%), most frequently hematological (n=9) or renal (n=3) (Table 2). In four patients, the acute hematological toxicity persisted beyond the time of PRRT and was thus included as long-term toxicity as well. Another 15 patients

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Table 3 PRRT response (n = 114) and outcomes (n = 149) in GEP NEN G3.

	CR (%)	**PR** (%)	**SD** (%)	**PD** (%)	**PFS** (m) (95% CI)	**OS** (m) (95% CI)	
All patients	1 (1)	47 (41)	43 (38)	23 (20)	14 (10.4–17.6)	29 (23.3–34.7)	
Performance status							[a]
0	1 (2)	21 (36)	26 (45)	10 (17)	**16 (11.0–21.0)**	**39 (28.1–49.9)**	
1	0	17 (53)	8 (25)	7 (22)	**14 (8.2–19.8)**	**23 (16.2–29.8)**	
2	0	3 (38)	2 (25)	3 (38)	**3 (0–6.2)**	**4 (0–12.6)**	
SRI tumor uptake							
≤Liver	1 (9)	3 (27)	4 (36)	3 (27)	16 (7.9–24.1)	25 (8.6–41.4)	
>Liver	0	44 (43)	38 (37)	20 (20)	14 (10.0–18.0)	29 (21.6–36.4)	
Primary tumor site							
Pancreas	0	32 (48)	23 (34)	12 (18)	14 (10.4–17.6)	29 (21.7–36.3)	
Gastrointestinal	0	11 (42)	9 (35)	6 (23)	10 (0–21.2)	31 (7.5–54.5)	
Unknown	1 (5)	4 (19)	11 (52)	5 (24)	16 (8.4–23.6)	29 (11.4–46.6)	
Differentiation							[a]
Well	0	19 (42)	23 (51)	3 (7)	**19 (13.9–24.1)**	**44 (25.2–62.8)**	
Poor	1 (2)	21 (41)	13 (25)	16 (31)	**8 (3.3–12.7)**	**19 (11.7–26.3)**	
Proliferation							[a]
Ki-67 21–54%	1 (1)	41 (41)	41 (41)	16 (16)	**16 (12.7–19.3)**	**31 (24.2–37.8)**	
Ki-67 ≥55%	0	6 (43)	2 (14)	6 (43)	**6 (3.0–9.0)**	**9 (4.5–13.5)**	
Differentiation and proliferation							[a]
NET G3	0	18 (42)	22 (51)	3 (7)	**19 (14.4–23.6)**	**44 (25.3–62.7)**	
NEC; Ki-67 21–54%	1 (3)	16 (41)	12 (31)	10 (26)	**11 (5.4–16.6)**	**22 (16.0–28.0)**	
NEC; Ki-67 ≥55%	0	5 (45)	1 (9)	5 (45)	**4 (0.8–7.2)**	**9 (1.6–16.4)**	

Response determined according to response evaluation criteria in solid tumors v 1.1. Statistically significant results are in bold text.
[a]Denotes statistically significant difference in PFS and OS with P-values shown in Figs 2 and 3.
ALP, alkaline phosphatase; CI, confidence interval; CR, complete response; GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; LDH, lactate dehydrogenase; m, months; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SRI, somatostatin receptor imaging.

without any acute severe toxicity developed long-term hematological (n=11), renal (n=3) or not specified (n=1) grade 3–4 toxicity. For first, second and later line of treatment, 5 (17%), 16 (26%) and 13 (23%) patients had grade 3–4 toxicity, respectively. With ^{177}Lu 24 (24%), ^{90}Y 7 (21%) and combined ^{177}Lu/^{90}Y 3 (25%) patients had grade 3–4 toxicity, respectively. Renal grade 3–4 toxicity occurred in two patients (6%) treated with ^{90}Y and four patients (4%) treated with ^{177}Lu.

Discussion

To the best of our knowledge, this is the largest study to assess the outcome after PRRT in patients with advanced high-grade GEP NEN. The majority of the patients had radiological progressive disease at the start of PRRT; RR was 42% and DCR was 69% for evaluable patients. A promising median PFS of 14 months and median OS of 29 months was found. Hematological or renal grade-3–4 toxicity occurred in 17% of patients, not more than that observed for other patient groups given PRRT. These results suggest that PRRT can be effective and tolerable in high-grade GEP NEN patients.

Comparison with standard treatment

The current recommendations for first-line treatment of advanced GEP NEC are systemic platinum-based chemotherapy giving a RR of 30%, PFS 4–5 months and OS 11 months (Sorbye *et al.* 2013, Yamaguchi *et al.* 2014, Heetfeld *et al.* 2015, Walter *et al.* 2017). Second-line treatment for NEC is usually of short benefit with an estimated PFS of 3–4 months (Welin *et al.* 2011, Hentic *et al.* 2012, Olsen *et al.* 2012, 2014, Hadoux *et al.* 2015, Walter *et al.* 2017). The Nordic NEC study showed a poorer RR to platinum-based chemotherapy in patients with Ki-67 <55% (RR: 15%) compared to patients with a Ki-67 ≥55% (RR: 42%) (Sorbye *et al.* 2013). Data for advanced NET G3 are generally scarce; however, RR to platinum-based chemotherapy is low (0–17%) with a short PFS (2.4 months) (Sorbye *et al.* 2018). Median survival is reported to be more than 40 months but as data are presented as a mixture of stages, results are difficult to interpret (Velayoudom-Cephise *et al.* 2013, Heetfeld *et al.* 2015, Hijioka *et al.* 2017, Sorbye *et al.* 2018). In a high-grade GEP-NEN population of 136 patients, median survival from time of first diagnosis was best for NET G3 (43.6 months), intermediate for NEC with a Ki-67

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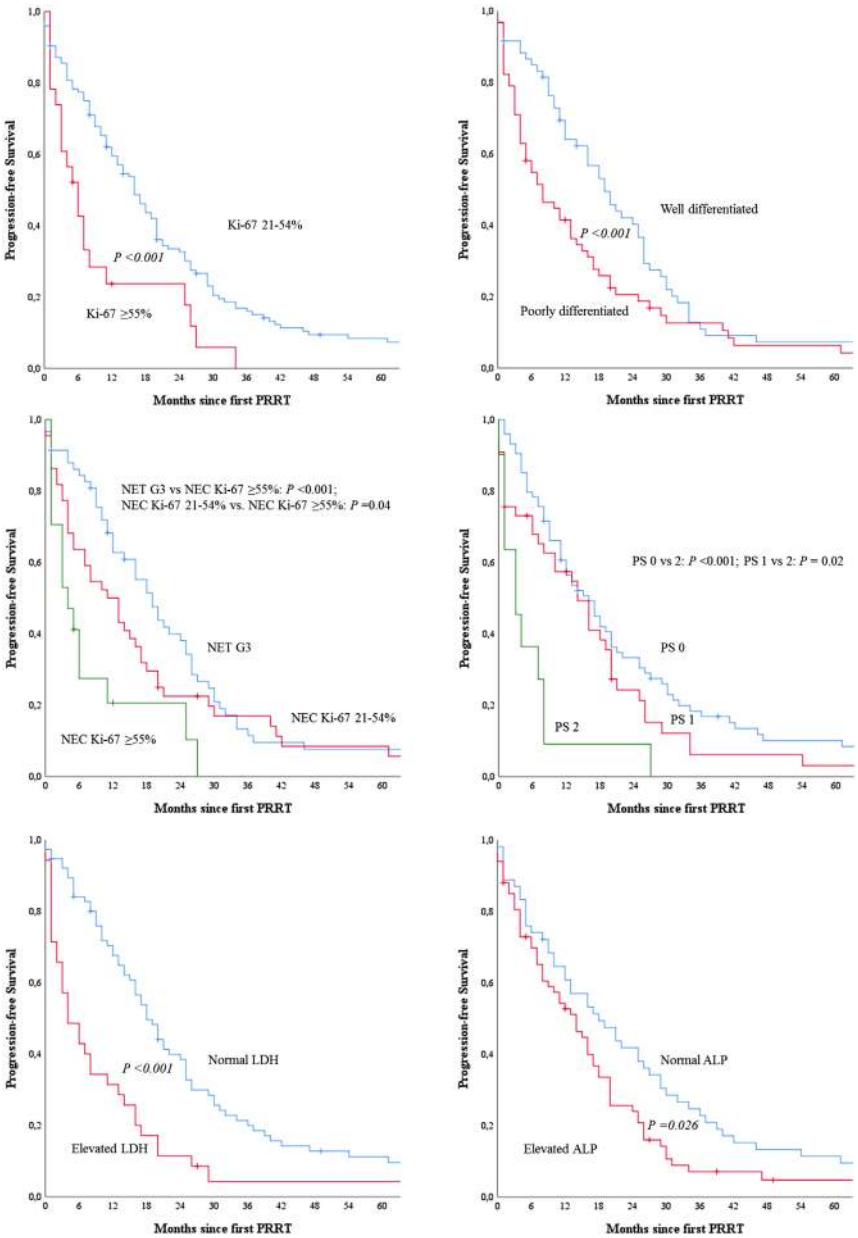

Figure 2
Kaplan-Meier curves of PFS for 149 patients with GEP NEN G3 treated with PRRT. Stratification by Ki-67 index (n = 148), differentiation (n = 122), performance status (PS) (n = 126), combined Ki-67 index and differentiation (n = 119), LDH (n = 111) and ALP (n = 121), respectively. PFS, progression free-survival; GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; PRRT, peptide receptor radionuclide therapy. A full colour version of this figure is available at https://doi.org/10.1530/ERC-18-0424.

21–54% (24.5 months) and 5.3 months for NEC cases with a Ki-67 ≥55% (Milione *et al*. 2017). A combination of capecitabine and temozolomide has been suggested for patients with well-differentiated tumor morphology and a Ki-67 21–54%, but data are scarce (Heetfeld *et al*. 2015, Garcia-Carbonero *et al*. 2016, Sorbye *et al*. 2018). In our cohort, half the patients were treated with SSA either before and/or after PRRT. SSA is not recommended for high-grade NEN, but may be explained by the selection of patients with a positive SRI or use of SSA after PRRT in general.

Cross-trial comparisons are difficult as well as evaluation of the benefit of PRRT without a control arm. However, a RR of 42% and DCR of 69% indicate that PRRT has an effect in our cohort. No differences in RR were observed in subgroups according to both well vs poor differentiation and Ki-67 21–54% vs Ki-67 ≥55%, as RR was approximately 40% in all subgroups. It may be that the efficacy of PRRT mediated by radiation is less sensitive to the degree of differentiation and rate of proliferation as long as the somatostatin receptor target is present on the tumor cells. The benefit of platinum-based chemotherapy seems to be more dependent on a high degree of proliferation, as evident in the Nordic NEC study (Sorbye *et al*. 2013). As most of our patients had radiologically progressive disease at the start of PRRT,

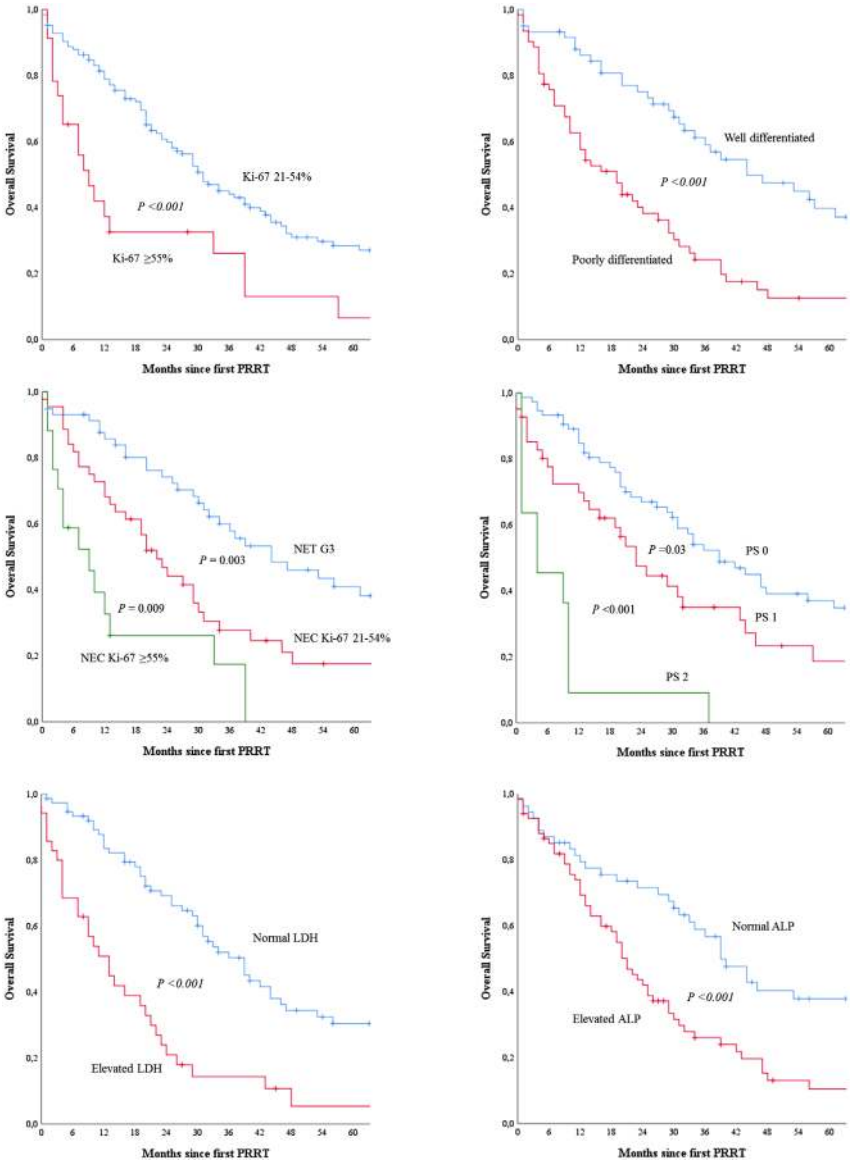

Figure 3
Kaplan-Meier analysis of OS for 149 patients with GEP NEN G3 treated with PRRT. Stratification by Ki-67 index (n = 148), differentiation (n = 122), performance status (PS) (n = 126), combined Ki-67 index and differentiation (n = 119), LDH (n = 111) and ALP (n = 121), respectively. OS, overall survival; GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; PRRT, peptide receptor radionuclide therapy. A full colour version of this figure is available at https://doi.org/10.1530/ERC-18-0424.

a PFS of 14 months indicates that PRRT seems to benefit many patients. Interestingly, no differences in RR, PFS and OS were evident in our cohort in regard to the line of treatment. Differentiation, Ki-67, PS, LDH and ALP were all significantly correlated to OS, as shown in previous studies (Sorbye *et al*. 2013, Lamarca *et al*. 2017). However, the true benefit of PRRT for PFS and especially OS is not possible to decide without a prospective randomized trial, which will be difficult to perform in such a rare disease. Since PRRT would seem most likely as a therapeutic option in NET G3, a prospective randomized trial comparing PRRT vs chemotherapy (temozolomide/capecitabine) in this population (or NEN G3 with a Ki67 <55%) is essential. Data are awaited to clarify whether concurrent chemotherapy to PRRT should be considered (ClinicalTrials.gov: NCT02736448).

Comparison with previous PRRT data in NEN G3 and classification

Three single-center retrospective studies recently reported the outcome of PRRT in NEN with a high Ki-67 and SRI tumor uptake >liver. An Australian study (Thang *et al*. 2018) assessed 28 patients with NEN and Ki-67 >20% (median Ki-67: 32.5%). The majority received PRRT with concurrent chemotherapy. The RR was 35%, PFS 9 months and OS 19 months for all patients. According to Ki-67 index PFS (12 vs 4 months) and OS (46 vs 7 months) differed for Ki-67 ≤55% and Ki-67 >55%.

Table 4 Univariate analyses of predictors for PFS and OS in 149 GEP NEN G3 patients treated with PRRT.

Covariate	PFS		OS	
	Hazard ratio (95% CI)	*P*-Value	Hazard ratio (95% CI)	*P*-Value
Age	1.00 (0.99–1.02)	0.84	1.01 (0.99–1.03)	0.20
Male	0.96 (0.68–1.34)	0.79	0.78 (0.53–1.1)	0.19
Performance status 0	1		1	
Performance status 1	1.36 (0.91–2.04)	0.14	**1.65 (1.04–2.63)**	**0.04**
Performance status 2	**3.53 (1.83–6.83)**	**<0.001**	**6.84 (3.40–13.76)**	**<0.001**
SRI ≤ liver	1.17 (0.67–2.04)	0.59	0.79 (0.40–1.57)	0.50
Primary tumor site (unknown primary)	1		1	
Gastrointestinal	1.13 (0.65–1.95)	0.67	0.75 (0.41–1.39)	0.36
Pancreas	1.29 (0.80–2.07)	0.30	0.83 (0.50–1.37)	0.46
Poorly differentiated	**1.62 (1.11–2.36)**	**0.01**	**2.55 (1.62–4.02)**	**<0.001**
Ki-67 ≥55%	**2.15 (1.34–3.47)**	**0.002**	**2.48 (1.51–4.06)**	**<0.001**
Differentiation and proliferation (NET G3)	1		1	
NEC; Ki-67 21–54%	1.38 (0.91–2.07)	0.13	**2.06 (1.26–3.39)**	**0.004**
NEC; Ki-67 ≥55%	**2.81 (1.55–5.11)**	**0.001**	**4.77 (2.51–9.06)**	**<0.001**
Line of treatment (first line)	1		1	
Second line	1.08 (0.69–1.69)	0.73	1.04 (0.63–1.71)	0.87
Later line	0.79 (0.50–1.24)	0.31	0.86 (0.52–1.42)	0.55
Elevated plasma-LDH	**2.35 (1.54–3.59)**	**<0.001**	**3.14 (1.96–5.02)**	**<0.001**
Elevated plasma-ALP	**1.53 (1.04–2.24)**	**0.03**	**2.21 (1.42–3.45)**	**<0.001**

Statistically significant results are in bold text.
ALP, alkaline phosphatase; CI, confidence interval; GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; LDH, lactate dehydrogenase; NEC, neuroendocrine carcinoma; NET G3, neuroendocrine tumor grade 3; OS, overall survival; PFS, progression free-survival; PRRT, peptide receptor radionuclide therapy; SRI, somatostatin receptor imaging.

A German study (Zhang *et al*. 2018) assessed 69 patients with GEP NEN and Ki-67 index >20% (median Ki-67, 30%). In their study, approximately one-third received concurrent chemotherapy – the effect hereof was reported as uncertain. The RR was 31%, DCR 78%, PFS 10 months and OS 20 months. According to Ki-67 index PFS (11 vs 4 months) and OS (22 vs 7 months) differed for Ki-67 ≤55% and Ki-67 >55%. An Italian study (Nicolini *et al*. 2018) assessed 33 patients with GEP NEN and Ki-67 index of 15–70% (median Ki-67: 25%). The RR was 6%, PFS 23 months and OS 52.9 months. Overall, in our study we found similar results: PFS (16 vs 6 months) and OS (31 vs 9 months) differed significantly in patients with Ki-67 <55% vs Ki-67 ≥55%.

In general, the likelihood of somatostatin receptor expression on neuroendocrine cells decreases with increasing grade of tumor, whereas the opposite applies for FDG uptake (Binderup *et al*. 2010, Hicks *et al*. 2017). NET G3 seems to have a positive SRI uptake in 70% of cases, whereas for NEC the figure is more likely 30% (Sorbye *et al*. 2013, 2018, Velayoudom-Cephise *et al*. 2013, Heetfeld *et al*. 2015, Raj *et al*. 2017). Preliminary studies have also shown the effectiveness of PRRT in patients with a more aggressive grade NEN with ^{18}F-FDG and SRI uptake (Kashyap *et al*. 2015). Patients with concordant ^{18}F-FDG and SRI-avid lesions may be more radiosensitive by having a high proliferative fraction. Few of the patients in our cohort had ^{18}F-FDG PET/CT data available limiting further analysis.

As previously reported (Basturk *et al*. 2015), the grading of NEN according to Ki-67 may be optimized by further sub-classification of patients with Ki-67 >20%. In the current study of patients graded as NEN G3 based on Ki-67, nearly half the patients had well-differentiated tumor morphology. The majority of patients with well-differentiated tumors also had Ki-67 21–54%. There was a marked difference in outcomes in our cohort when comparing subgroups based on tumor morphology: PFS (19 vs 8 months) and OS (44 vs 19 months) differed significantly comparing well-differentiated vs poorly differentiated neoplasms.

Toxicity

In our study, 26 patients (17%) had either acute or long-term grade 3–4 renal or hematological toxicity. This is similar to that reported in other larger retrospective analysis of patient groups given PRRT (Kwekkeboom *et al*. 2008, Imhof *et al*. 2011), although in NETTER-1, no evidence of renal adverse effects was observed in patients treated with ^{177}Lu (Strosberg *et al*. 2017). We observed renal toxicity both in patients treated with ^{90}Y and ^{177}Lu.

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Table 5 Multivariate Cox regression analysis of predictors for PFS and OS in 75 GEP NEN G3 patients treated with PRRT.

Covariate	PFS		OS	
	Hazard ratio (95% CI)	*P*-Value	Hazard ratio (95% CI)	*P*-Value
Age	**0.98 (0.95–1.00)**	**0.045**	0.99 (0.96–1.02)	0.42
Male	1.53 (0.85–2.74)	0.16	1.05 (0.53–2.10)	0.89
Performance status 0	1		1	
Performance status 1	**2.57 (1.33–4.93)**	**0.005**	**2.35 (1.13–4.89)**	**0.02**
Performance status 2	3.42 (0.90–13.06)	0.07	**4.20 (0.98–18.01)**	**0.05**
SRI ≤ liver	0.72 (0.13–4.03)	0.70	0.43 (0.04–4.33)	0.47
Primary tumor site (unknown primary)	1		1	
Gastrointestinal	0.80 (0.32–2.02)	0.64	0.78 (0.26–2.37)	0.66
Pancreas	0.66 (0.28–1.57)	0.35	0.46 (0.18–1.22)	0.12
Poorly differentiated	1.69 (0.88–3.23)	0.11	**2.92 (1.31–6.50)**	**0.009**
Ki-67 ≥55%	1.11 (0.51–2.42)	0.80	1.97 (0.83–4.66)	0.13
Line of treatment (first line)	1		1	
Second line	0.76 (0.38–1.54)	0.46	1.55 (0.70–3.43)	0.28
Later line	1.04 (0.48–2.27)	0.91	1.77 (0.67–4.65)	0.25
Elevated plasma-LDH	**2.66 (1.29–5.49)**	**0.008**	**2.61 (1.16–5.90)**	**0.02**
Elevated plasma-ALP	**2.24 (1.22–4.09)**	**0.009**	**2.79 (1.42–5.49)**	**0.003**

Due to missing values for one or more of the covariates, 74 patients were not included in the model. Statistically significant results are in bold text.
ALP, alkaline phosphatase; CI, confidence interval; GEP NEN G3, gastroenteropancreatic neuroendocrine neoplasm grade 3; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression free-survival; PRRT, peptide receptor radionuclide therapy; SRI, somatostatin receptor imaging.

Furthermore, we found similar frequency of toxicity for patients receiving PRRT as first line vs later line of treatment.

Limitations

High-grade GEP NEN patients treated with PRRT are probably highly selected on factors as being positive on SRI imaging and having a rather low median Ki-67 compared to the NEN G3 group as a whole. RR, PFS and OS should be interpreted carefully in light of the retrospective design of the study. However, most of our patients were classified as having radiological progression of disease at the start of PRRT, and approximately half were based on RECIST. The rate of side effects of PRRT in our analysis was in line with that previously reported for PRRT, but toxicity reports in a retrospective study must be interpreted cautiously. Pathologist reports were mainly from NET expert centers and reclassification was done in reports with missing data when sections were available. Though, a general problem is that the distinction between well and poor differentiation is not standardized (Tang *et al*. 2016) and at present it is only determined based on tumor morphology (Kloppel *et al*. 2017). Future studies possibly adding molecular data on DAXX, ATRX (loss of expression in well-differentiated pancreatic tumors) and Rb1, KRAS and p53 (expressed in poorly differentiated tumors), could assist further to classify these tumors (Sorbye *et al*. 2018).

Conclusion

This large retrospective multicenter study is at present the most comprehensive report on which to base treatment decisions regarding the use of PRRT in high-grade GEP NEN. It shows promising RR, DCR, PFS and OS and acceptable toxicity after PRRT in patients with mainly progressive disease. This suggests that PRRT is active and potentially effective in patients with GEP NEN G3. Awaiting further data, PRRT may therefore be a treatment option for GEP NEN G3 patients.

Declaration of interest
E A C has received paid travel to meetings by Novartis and Ipsen. H A has received a grant from Novartis and honorarium from Ipsen and Novartis for oral presentations. A R has received honoraria for presentations and attendance at advisory board meetings from Novartis and Ipsen. A F has received funding from Ipsen, Novartis, AAA and SIRTeX. U K has received funding from 'Internationaliseringspuljen', Institute for Clinical Medicine, University of Copenhagen, Denmark to perform research in NEC.

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