Mid-PRRT Response Predicts Overall Outcome in Patients with Neuroendocrine Neoplasms

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Research Article

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Abstract

Introduction – Patients with advanced well differentiated neuroendocrine neoplasm (WD-NEN) often required both peptide receptor radionuclide therapy (PRRT) with subsequent chemotherapy. Although preserving bone marrow function is vital, there are no mid-PRRT response predictors, to limit radiation exposure in patients with low predicted success rate.

Purpose – To assess the utility of mid-PRRT response as a predictor for overall outcome in patients with WD-NEN.

Methods - A retrospective study of WD-NEN patients that underwent ≥4 PRRT cycles. Data gathered included demographics, tumor grade, stage, and treatment response (partial response [PR], stable disease [SD] or progressive disease [PD]) evaluated by 68Ga-DOTATATE positron emission tomography (PET)/computerized tomography (CT) pretreatment, one month after 2^{nd} and 4^{th} treatment cycle, six months after 4^{th} cycle and at last follow-up.

Results - Thirty-one patients (51.6% women, age at diagnosis 62.8±1.8 years), with pancreatic (PNEN, n=15), small intestine (SiNEN, n=9), lung (LNEN, n=2) or other (n=5) NEN received PRRT, resulting in PR (n=14), SD (n=13) and PD (n=1). Patients with PNEN had superior response vs. SiNEN ($p<0.05$). Patients with PR at mid-treatment had higher PR rates after PRRT completion than those with SD ($p=0.004$), but not six months post-PRRT or at last follow-up ($p>0.05$ for both). On multivariable model, adjusted for age, grade and primary site, PR at mid-treatment evaluation was associated with 10.7 adjusted odds ratio for additional PR at PRRT completion ($p=0.02$).

Conclusion - Mid-PRRT assessment predicts subsequent response to PRRT in WD-NEN patients, allowing personalized management and reduced bone-marrow toxicity in high-risk patients.

Introduction

Neuroendocrine neoplasms (NEN) are rare tumors, with increasing frequency in the past decades, reaching an annual incidence of 6.9 per 100,000 persons [1]. NENs were previously thought to originate from cells of neural crest origin [2], and may develop at various organs, the most common are of the gastro-entero-pancreatic (GEP) and lung origin [3]. Some of these tumors are functional with hormonal secretory ability that can cause various endocrine syndromes such as the carcinoid syndrome (including diarrhea, flushing, wheezing and right sided cardiomyopathy [4, 5]), hypoglycemia (due to insulin secretion in insulinomas [6]). Histopathological grading in NEN is based on cells morphology, and on mitotic rate and percentage of positive staining for the proliferation index Ki67 [7]. For lung NENs, grade is based on mitotic rate and presence of necrosis [8].

The management of patients with metastatic and/or unresectable NENs is composed of multi-modality intervention, mainly including medical and radionuclide intervention with somatostatin analogues (SSA), everolimus (inhibitor of the mammalian target of rapamycin, mTOR), tyrosine kinase inhibitors, peptide radioligand receptor therapy (PRRT) or chemotherapy [9]. PRRT is an efficacious treatment for advanced NEN, yielding prolonged progression free survival (PFS) compared with high-dose SSA treatment in patients with well-differentiated small-intestine NEN [10] in the NETTER-1 trial. PRRT is a mainstay intervention also for NEN of other primary sites, and is well established in the current clinical management guidelines [11, 12]. The mechanism of action of PRRT is based on combining a SSA-derivative with a beta-emitting radio tracer, administered intravenously in four cycles with two months intervals in between [13]. Common short-term side effects of PRRT include nausea and fatigue [10]. Long-term toxicity of PRRT is rare, and includes acute leukemia in 0.7% and myelodysplastic syndrome in 1.5% of patients, and extremely rare renal or hepatic failure [14]. While the rate of these events is quite low in some studies, when PRRT is combined with chemotherapy the rate of myeloid neoplasms increases to 6.7% [15].

The chances for reaching complete remission in PRRT is low, reported in one patient (1%) in the NETTER-1 trial [10]. Hence, most patients will require further systemic therapy, often chemotherapy, following PRRT. It is therefore important to have predictive parameters during PRRT treatment for response to PRRT, to identify which patient will have a beneficial outcome that justify completion of PRRT treatment. However, there are few known predictive factors that are specific for PRRT response. The first is tumor pretreatment avidity on somatostatin receptor scintigraphy [16], and in fact it is also a baseline requirement to demonstrate that all neuroendocrine lesions are DOTATATE-avid in order to allow PRRT treatment [13]. Surprisingly, a reduction in standardized uptake value (SUV) on ^{68}GaDOTATATE PET CT after 1st PRRT treatment [17] or after PRRT completion [18] is associated with prolonged (PFS). Another possible predictor is the combination of circulating transcriptome data with grade, showing high

sensitivity for PRRT response [19]. Chen et al [20] formalized a PRRT prediction model, demonstrating that baseline normal serum creatinine and an elevated serum chromogranin A levels, as well as previous chemotherapy treatment, were associated with a higher one year failure rate. However, in another study, previous chemotherapy treatment was associated with better PRRT outcome [21].

Overall, most of these markers may assist in predicting outcome based on pretreatment properties, but not based on reassessment during the ongoing treatment. Therefore, in this study we aimed to unravel predictive factors for favorable outcome of PRRT that can be utilized for reassessment during treatment.

Materials and Methods

This was a retrospective study based on a tertiary center database of patients that underwent PRRT for stage IV neuroendocrine tumors (NENs) between the years 2019–2023. Inclusion criteria were completion of a minimum of four PRRT treatments, and presence of at least one measurable NET lesion.

Data collected included demographic characteristics (current age, age at diagnosis, and sex), NEN type/primary site (pancreas, small intestine and other for kidney, testis and lung NENs), NEN functional status (e.g., non-functional, carcinoid syndrome, insulinoma), grade (differentiation, percentage of positive staining for Ki67, mitotic index, and for lung NEN presence of necrosis), stage (based on the 8th Edition of the American Joint Committee on Cancer [7]), previous pharmacological treatment, and concurrent treatment with SSA during PRRT treatment. In addition, imaging results were acquired at several time points: prior to 1st PRRT, after 2nd PRRT, after 4th PRRT treatment, six months after 4th PRRT treatment and at last follow up. Preferred imaging modality was ^{68}Ga-DOTATATE positron emitting tomography (PET) with arterial-phase contrast enhanced computerized tomography (CT), that was available for all patients at all time points up to six months from last PRRT treatment. For the last follow-up timepoint we used ^{68}Ga-DOTATATE PET/CT and if not available either contract enhanced CT or contrast enhanced magnetic resonance imaging (MRI). Imaging results were based on expert radiologist reports or on the interpretation in the multidisciplinary team meeting, and were categorized to stable disease (SD), partial response (PR), complete response (CR), or progressive disease (PD).

Statistical analysis

The statistical analysis was performed using SPSS Statistics (version 20.0.0, IBM, 2011, Armonk, NY, USA). Continuous variables with normal distribution were compared with the Student's t-test, and categorical parameters were compared using the chi-square test or Fisher's exact test. Continuous variables are presented as mean ± standard error of the mean (SEM) unless stated otherwise, and categorical parameters are presented as n (%). Non-parametric tests were used as appropriate. Two-tailed p-value < 0.05 was set as a threshold for statistical significance. Multivariate model analysis was carried out for predicting treatment outcome, the model was adjusted for age, grade and tumor type, and mid-treatment (after 2nd PRRT treatment) outcome. Figures were produced on R Studio (RStudio, PBC, Boston, MA, version 2023.03.1).

Results

A total of 31 patients (15 [48.4%] males) with NENs completed at least four PRRT treatments. Average age at NEN diagnosis was 62.8 ± 1.8 years (Table 1). Twenty-seven (87.1%) patients had G1/G2 NEN and four (12.9%) had G3 NEN. Only 29.0% of the patients had functional NEN, 19.4% suffered from carcinoid syndrome, 9.7% from insulinoma and 3.2% from gastrinoma. Most patients had gastro-entero-pancreatic (GEP) NEN, nine had small intestine NEN (SiNEN) and 15 had pancreatic NEN (PNEN). All patients had stage IV disease, and all NEN lesions were avid on ^{68}Ga-DOTATATE PET/CT at pre-PRRT evaluation. 26 (83.8%) patients were co-treated with a somatostatin analogue (SSA) during PRRT.

Table 1
Characteristics of patients with neuroendocrine neoplasm that completed at least four PRRT treatments.

	Patients characteristics
n	31
Female sex	16 (50.7%)
Age at diagnosis (years)	62.8 ± 1.8
Type (PNEN/SiNEN/Lung/Other)	15(48.4%)/9(29.0%)/2(6.5%)/5(16.1%)
Grade	
GEP NEN (G1/G2/G3)	8(25.8%)/19(61.3%)/4(12.9%)
LNEN (Typical/ Atypical)	1(50%)/1(50%)
Functional y/n	9(29.0%)/22(70.9%)
Hormonal hypersecretion syndrome (Carcinoid/Insulinoma/Gastrinoma)	6(19.4%)/3(9.7%)/1(3.2%)
Status after 4th PRRT treatment (SD/PR/PD)	13(46.4%)/14(50.0%)/1(3.6%)
Status 6 months after 4th PRRT treatment (SD/PR/PD)	12(60.0%)/6(30.0%)/2(10.0%)
Status at last follow-up (SD/PR/PD)	14(60.9%)/3(13.0%)/6(2.6%)
Received SSA treatment during PRRT	26(83.9%)
Received non-SSA medical treatment before PRRT	1(3.2%)

Continuous variables are reported as mean ± standard deviation, categorical variables are reported as n (%). Other NEN types included renal (n = 1), rectal (n = 2), testicular (n = 1), and unknown primary (n = 1) NEN. PRRT, peptide receptor radionuclide therapy; PNEN, pancreatic neuroendocrine neoplasms; SiNEN, small intestine neuroendocrine neoplasms; LNEN; lung neuroendocrine neoplasms; SD, stable disease; PR, partial response; PD, progressive disease; SSA, somatostatin analogues

After two PRRT treatments, 18 (58.1%) patients had partial response and 13 (41.9%) stable disease (Table 2, Fig. 1). There was no statistical difference between the groups of patients with SD or PR after two PRRT treatments in terms of age at NEN diagnosis, sex, grade, functionality of the tumors, or co-treatment with a SSA ($p > 0.05$ for all comparisons). However, patients with PNEN had a higher PR rate after two PRRT treatments compared with patients with SiNEN (80.0% vs 22.2%, respectively, $p = 0.005$) and after the 4th PRRT treatment (58.8% vs 12.5%, respectively, $p = 0.013$), but not six months after treatment completion (33.3% vs 0, $p > 0.05$) or at last follow-up (23.0% vs 0%, $p > 0.05$).

Table 2
Patients' characteristics compared according to response type after two PRRT treatments.

	Disease status after 2nd PRRT treatment		p value
	Partial response (n = 18 [58.1%])	Stable disease (n = 13 [41.9%])	
Female sex	9 (50%)	7 (53.8%)	0.83
Age at diagnosis (years)	62.3 ± 2.8	63.4 ± 2.09	0.77
Type (PNEN/SiNEN/LNEN/Other)	12(66.7%)/2(11.1%)/15.6%)/3(16.7%)	3(23.1%)/7(52.8%)/1(7.7%)/2(15.4%)	0.005*
Grade			
GEP NEN (G1/G2/G3)	3(16.7%)/13(72.2%)/2(11.1%)	5(38.5%)/6(46.2%)/2(15.4%)	0.13#
LNEN (Typical/ Atypical)	1(100%)/0(0.0%)	0(0.0%)/1(100.0%)	NS
Functional NEN	4(21.1%)/15(78.9%)	5(71.4%)/7(28.6%)	0.25
Hormone oversecretion syndrome (Carcinoid/Insulinoma/Gastrinoma)	1(5.3%)/2(10.5%)/1(5.3%)	4(30.8%)/1(7.7%)/0(0.0%)	0.98^
Response after 4th PRRT treatment (SD/PR/PD)	4(23.5%)/12(70.6%)/1(5.9%)	9(81.8%)/2(18.2%)/0(0.0%)	0.004$
SD/PR/PD 6 months after 4th PRRT treatment	6(46.2%)/5(38.5%)/2(15.4%)	6(85.7%)/1(14.3%)/0(0.0%)	0.17$
SD/PR/PD at last follow-up after 4th PRRT treatment	7(46.7%)/3(20.0%)/5(33.3%)	7(87.5%)/0(0.0%)/1(12.5%)	0.23$
SSA treatment during PRRT	15(83.3%)	11(84.6%)	0.92
Previous medical treatment other than SSA	1(5.6%)	0(0.0%)	NS

Continuous variables are reported as mean ± standard deviation, categorical variables are reported as n (%). Other NEN types included renal (n = 1), rectal (n = 2), testicular (n = 1), and unknown primary (n = 1) NEN. LNEN; lung neuroendocrine neoplasms; NS – nonsignificant; PRRT, peptide receptor radionuclide therapy; PNEN, pancreatic neuroendocrine neoplasms; SiNEN, small intestine neuroendocrine neoplasms; SD, stable disease; PR, partial response; PD, progressive disease; SSA, somatostatin analogues. *PNEN vs SiNEN; #G1 vs G2; $SD vs PR; ^Carcinoid vs insulinoma + gastrinoma.

Patients with PR after two PRRT treatments had a greater chance of having additional PR at the last two PRRT treatments compared to those with SD after two PRRT treatments (p = 0.004). Such association was not observed for treatment response six months after PRRT completion or at last follow-up (p = 0.17 and p = 0.23, respectively, Table 2).

Time to progression

Of the six patients that had PD after PRRT completion, median time to progression was 6.5 months (range, 4–8 months). At last follow-up, 19 patients had either SD (16 patients, median follow-up time 12 months, time range 2–32 months of follow-up) or had further PR (three patients, time range 4–10 months).

Multivariable analysis

On multivariable model (Fig. 2), adjusted for age, grade and tumor type (PNEN/SiNEN or other), mid-treatment outcome was independently associated with outcome after four PRRT treatments (adjusted odds ratio 10.75, 95% confidence interval 1.45–76.90, p = 0.02). However, such association could not be assessed six months after treatment and at last follow-up due to the low incidence of PR and variables convergence with grade at these time points.

Hematologic side effects

Of the 31 patients evaluated in this study, one patient developed chronic myelomonocytic leukemia (CMML) 18 months after PRRT completion and another patient developed reduced leukocyte count without evidence of MDS on bone marrow biopsy, with

subsequent improvement of blood count.

Discussion

In the current study, we investigated possible predictive markers for peptide receptor radionuclide therapy (PRRT) outcome in patients with advanced neuroendocrine neoplasms (NENs). A favorable response (partial response vs stable disease) after two PRRT treatments was predictive of a higher rate of partial response after completion of PRRT treatment, as demonstrated by multivariate model controlled for patients' age, grade and NEN type. In addition, a pancreatic NEN (PNEN) primary was associated with a higher rate of partial response compared with small intestine NEN (SiNEN) during and after PRRT treatment.

Previous studies have demonstrated the importance of functional imaging as a predictive factor for PRRT outcome. Baseline tumor avidity on ^{68}Ga-DOTATATE PET/CT before PRRT treatment is predictive of response [22], and in addition, reduction in the standardized uptake value on ^{68}Ga-DOTATATE PET/CT after 1st PRRT treatment is also associated with prolonged PFS [17]. However, to the best of our knowledge, this is the first study to evaluate and demonstrate that mid-treatment partial response is predictive of continued partial response at treatment's end. One should note that no formal guidelines recommend imaging during PRRT as a decision tool for continued treatment. The NETTER-1 trial, the first clinical trial to demonstrated efficacy of PRRT for mid-gut NEN, included imaging every 12 weeks in order to assess response [10], and the European Neuroendocrine Society (ENETS) guidelines only suggest evaluation by clinical response or imaging (somatostatin analogue PET/CT or SPECT) during PRRT [13]. While further research with a larger sample size and follow-up time is required to validate our results, adding imaging assessment during PRRT should be considered, as it might aid the clinical decision of whether to continue PRRT in the case of a patient with a borderline hematologic parameter during treatment.

An additional finding in this study is that a pancreatic tumor origin is also predictive of continued partial response during PRRT compared with small intestine origin. A favorable response to PRRT in PNEN was previously describe by Hasegawa et al [21], demonstrating that pancreatic origin is a favorable factor for lesion shrinkage after PRRT, while rectal NEN is associated with resistance to tumor reduction. Pancreatic NEN differ from SiNEN in several aspects, first, hormonal secretory syndromes differ markedly between the two, as carcinoid syndrome is prevalent in 20–30% of SiNEN with liver metastases [23] while under 1% of carcinoid syndromes are of PNEN origin [11]. Second, a larger proportion of PNEN develop as part of multiple neoplasia syndromes compared to rare reports in SiNEN [24]. In addition, the somatic genetic landscape of PNEN comprise an almost three times higher mutation rate in PNEN vs. SiNEN with specific driver mutations in PNEN (most commonly inactivation of *MEN1* and *ARTX*/*DAXX*), while SiNEN show mainly chromosomal alterations (loss of parts of chromosome 8 and 18, gains of 4, 5 and 20) [24, 25]. Overall, the striking difference in genetic stability between PNEN and SiNEN might lead to a better response to PRRT seen in PNEN, as a higher mutation rate and genomic instability renders the tumor more susceptible to certain pharmacological treatments [26, 27].

This study has several limitations. First, it is a retrospective study that includes only patients with metastatic disease and very few patients with lung NEN, thus results of this study might not be applicable to locally advanced NENs or to lung NEN. Second, due to the relatively small cohort, we were not able to statistically assess the validity of mid-treatment response as a predictor for long-term (six months from PRRT completion or at last follow-up) response. Finally, high-grade NEN were not represented in this study but for a few cases. However, as there is no published randomized controlled trials demonstrating PRRT efficacy in G3 NEN yet, the low proportion of high-grade NEN in this study is in fact predictable.

To conclude, mid-treatment response to PRRT might serve as predictor for PRRT outcome. This finding is important as it is a readily available tool for disease evaluation and decision-making during treatment, thus providing data to either support or cease continued PRRT treatment.

Declarations

Statements and declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Reut Halperin and Amit Tirosh. The first draft of the manuscript was written by Reut Halperin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

The study was approved by the ethics committee of the Chaim Sheba Medical Center (SMC-18-5735 and SMC-18-5674).

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Figures

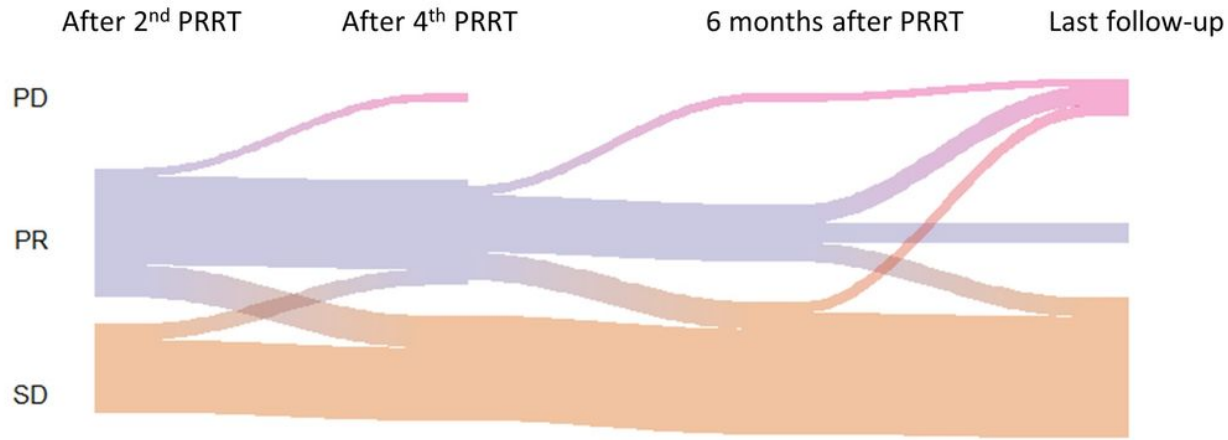

Figure 1

River-plot of patients response at mid-PRRT, post 4th PRRT and at last follow-up demonstrate continuity of patient population with stable disease mid-treatment and post-treatment, and with partial response at mid-treatment and additional partial response in the additional two cycles

PD, progressive disease; PR, partial response; PRRT, Peptide-receptor radionuclide therapy; SD, stable disease

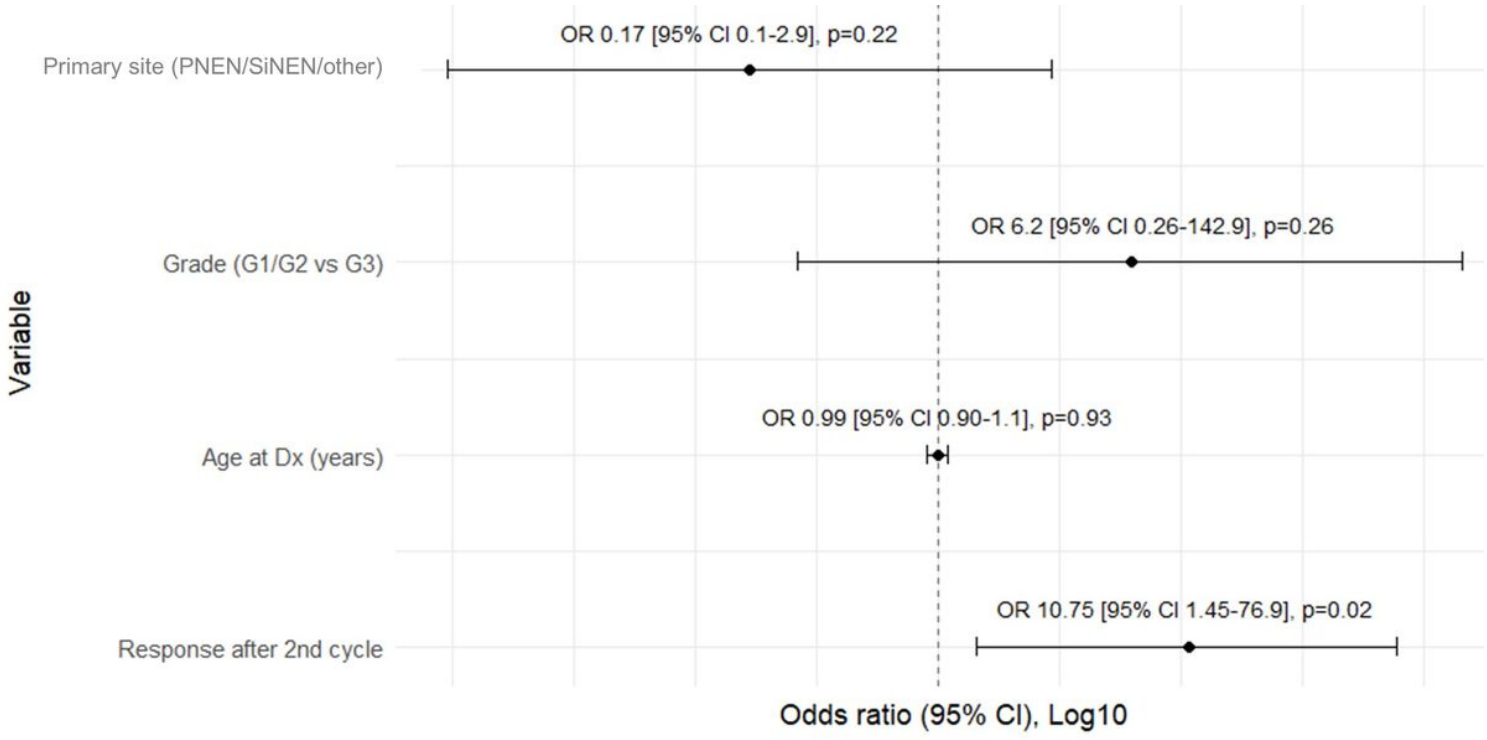

Figure 2

Response to PRRT in patients with neuroendocrine neoplasms after 2 cycles predics additional response at subsequents treatments. Multivariable analysis showing the odds ratio (OR) for additional partial response (PR) after mid-treatment PR, adjusted for sex, age at diagnosis and tumor type and grade. Dx, diagnosis; PNEN, pancreatice neuroendocrine neoplasm; PRRT, Peptide-receptor radionuclide therapy; SiNEN, small intestine neuroendocrine neoplasm