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Clinical characteristics and treatment patterns of patients with gastroenteropancreatic neuroendocrine neoplasia in Germany receiving peptide receptor radionuclide therapy

A real-world data registry-based study

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Abstract

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare malignancies deriving from the endocrine system in the gastrointestinal tract including the pancreas. Prognosis is greatly heterogenous due to its dependency on various factors, most importantly stage and differentiation. Several studies report an alarming rise in incidence in the past decade. Despite there being some therapeutical options, best therapy sequence still needs to be defined, particularly for unresectable and/or intermediate and high-grade NENs. Peptide receptor radionuclide therapy (PRRT) was approved in Europe and USA in 2017 and 2018, respectively. Studies with real-world systematic data on characteristics and treatment patterns of PRRT-receiving patients was non-existent at the time of this writing. In this retrospective study, we identified within the German NET-Registry 203 patients diagnosed with GEP-NEN having received PRRT from 1995 to 2023. We assessed general clinical patient characteristics, disease-specific characteristics, treatments and outcomes. To obtain a more up-to-date picture of treatment modalities and outcomes, a subgroup of the study population was allocated to the "therapy cohort," defined by patients with date of first diagnosis between 2010 and 2023 (open cohort). Mean age of the study population was 58 years (SD 12 years) with 51.7% being men. Most patients had a WHO performance score of 0 to 1 (41.4% and 50.5%, respectively). Most NEN cases were of small intestine/pancreatic origin (46.3% and 45.3%, respectively) and displayed well/moderate differentiation (55.3%). Ki-67 was generally within the 3% to 20% range (57.92%). Most patients presented with metastasis at diagnosis (73.9%). Somatostatin analogs (SSAs), chemotherapy and surgery were the most common non-PRRT therapy options (65.3%, 60.2%, and 50.0%, respectively). PRRT was most often applied as third- or second-line therapy (42.3% and 36.6%, respectively), usually after surgery and/or SSA treatment. As PRRT had been administered using different regimens, tumor response evaluation showed mixed responses. Given the low sample size and considerable amount of missing response data, no correlation analysis between PRRT sequencing and tumor response could be performed. Overall, the clinical characteristics and treatment patterns tend to follow trends observed in other studies or medical guidelines. Finally, this study presents real-world data that more accurately describes GEP-NEN disease in Germany and treatment modalities after PRRT's approval.

Abbreviations: CUP = cancer of unknown primary, EMA = European Medicines Agency, ESMO = European Society for Medical Oncology, G1, G2, G3 = grade 1, 2 and 3, GEP = gastroenteropancreatic, IFN-alpha = interferon alpha, MTT = moleculary targeted therapy, NEC = neuroendocrine carcinoma, NEN = neuroendocrine neoplasm or neoplasia, NET = neuroendocrine tumor, pNEN = pancreatic neuroendocrine neoplasm, pNET = pancreatic neuroendocrine tumor, PRRT = peptide receptor radionuclide therapy, SD = standard deviation, SSA = somatostatin analog, SSR = somatostatin receptor, TSF = time to strategy failure, WHO = World Health Organization.

Keywords: epidemiology, gastroenteropancreatic neuroendocrine neoplasms, GEP-NEN, GEP-NET, oncology, PRRT, registry, treatment patterns

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

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board at Charité Mitte, Berlin, Germany, with approval of the updated web-based version on January 31, 2022 (EA1/370/21). In addition, obtainment of local ethics committee approval was mandatory for every participating center. All patients signed an informed consent form.

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1. Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a rare type of malignant neoplasia that derive from neuroendocrine cells in the gastrointestinal tract including the pancreas. The European Society for Medical Oncology (ESMO) claims that 50% of cases are of intestinal origin and 30% are of pancreatic origin.[1] GEP-NENs account for approximately two-thirds of all NEN cases and have been reported to have an overall annual incidence of 3.5 to 4.8 per 100,000 population in the past decade (incidences observed in England, Germany, Iceland and United States).[2–4] Compared to reported incidences from the 1990s and 2000s, there has been a clear global rise over time, for the most explained by increased health care utilization and improved diagnostics. However, other factors are to be considered including as-of-yet undetermined environmental factors and underlying patient biology.[3] Men tend to be slightly more affected than women and face worse prognosis.[1] Based on the current understanding of the disease, most cases arise sporadically, however a small percentage is associated to hereditary predisposition syndromes, such as multiple endocrine neoplasia type 1, tuberous sclerosis, Von Hippel-Lindau's disease or neurofibromatosis type 1, which tend to be detected earlier than the sporadic cases. The reported frequency of hereditary backgrounds (multiple endocrine neoplasia type 1, Von Hippel-Lindau's disease) is about 5%.[5]

GEP-NENs can be functional or nonfunctional based on whether the patient presents with clinical signs due to hormonal hypersecretion. The majority of GEP-NENs do not secrete enough active hormones or biogenic amines (hormone-like substances), and are typically diagnosed at a later stage with symptoms related to mass effects or distant metastases.[6] Rarely, nonfunctional tumors become hormonally active.[7,8] The long period between onset of symptoms and NEN diagnosis, as well as the indolent nature of several NENs, which makes reaching an accurate diagnosis challenging, has been previously discussed.[9,10]

The 2019 World Health Organization (WHO) classification of digestive system tumors provides grading of GEP-NENs in terms of the growth rate (based on Ki-67 index or mitotic rate), distinguishes between well-differentiated neoplasms which are called neuroendocrine tumors (NETs) and poorly differentiated neoplasms which are called neuroendocrine carcinomas (NECs), and allows for classification of NENs of mixed neuroendocrine and non-neuroendocrine components. Importantly, GEP-NENs that are morphologically well-differentiated and often identical to grade 1 (G1) or grade 2 (G2) NET but feature a high Ki-67 index (>20%) were recognized in this review. These were classified as NET grade 3 (G3).[2]

Prognosis is mostly influenced by tumor stage and grade, however additional significant prognostic factors include age at diagnosis, lesion size, levels of biomarkers (e.g., chromogranin A, Ki-67 index) and clinical symptoms.[1,11–15] The overall 5-year survival rate in GEP-NET is around 70%, ranging from 38% for pancreatic NETs (pNETs) to 89% for rectal NETs, and nearly 100% for small gastric NETs. Patients with locally advanced/metastatic GEP-NETs have a reported median survival time of 12.7 years from the start of first-line therapy. Specifically in pNET, the median survival time is approximately 11.3 years in cases of localized disease and 2.0 to 3.9 years in cases with distant metastases. For NETs in the small intestine, the reported median survival time is 9.3 years for patients with localized disease and 4.7 to 7.9 years when distant metastases are present.[16] In contrast, the clinical management of GEP-NECs poses a greater challenge: 5-year survival for localized carcinoma is 25% to 40%, immediate disease progression on first-line treatment is seen in up to 30% of cases and median progression-free survival is reaching only 4 to 5 months.[17]

Currently, surgery is the only curative therapy option for NEN. However, not all NEN cases are eligible for surgical resection. Advanced/metastatic NENs are often unresectable or may only be treated with debulking/palliative surgery and will require systemic therapy.[1] For higher grade, well-differentiated GEP-NETs there is no consensus on a gold standard for first-line therapy. The NETTER-2 trial attempts to fill this gap by assessing the efficacy of peptide receptor radionuclide therapy (PRRT) as a first-line therapy compared to treatment with somatostatin analog (SSA) and recently met its primary endpoint.[18] Other therapy options currently in use and appearing in different sequences are interferon alpha (IFN-alpha), chemotherapy and molecularly targeted therapies (MTTs) such as everolimus and sunitinib. Patients with liver metastases who are not eligible for complete surgical resection are advised to undergo vascular and ablative locoregional therapies, in addition to systemic treatment.[1]

PRRT consists of injections of radiolabeled somatostatin analogs in patients with cancers expressing sufficient somatostatin receptors (SSRs), which is usually the case of G1 and G2 NETs. These radiopharmaceuticals are built with 3 components: a radionuclide, a chelator and a somatostatin analog (peptide). It is an example of internal radiotherapy.[19] ^{177}Lu-DOTATATE (brand name Lutathera® from Novartis) was initially approved by the European Medicines Agency (EMA) in 2017 and by the Food and Drug Administration in 2018 for the treatment of adults with SSR-positive GEP-NETs. In 2024, the Food and Drug Administration expanded the indication to children aged 12 and older.[20] Currently, ^{177}Lu-DOTATATE is the only PRRT with marketing authorization, however other radiolabeled somatostatin analogs using components similar to the ones found in ^{177}Lu-DOTATATE are in use. In fact, physicians in Australia, Europe and the United States utilized PRRT at least a decade before its official approval based on compassionate use of experimental drugs.[21] PRRT is not only of interest for purely therapeutical purposes but also in the field of health economics and quality of life. Two recent studies based on real-world evidence of PRRT-receiving patients demonstrated lower overall costs, lower non-elective hospital stays and improved quality of life compared to other treatment arms.[22,23]

There are several new publications describing clinical characteristics and real-world treatment patterns for GEP-NEN patients,[16,24–29] however none focus specifically on PRRT-receiving patients with a wide range of GEP-NEN entities and different PRRT formulations, nor show in detail the treatment algorithms and outcomes after the first approved GEP-NET radiopharmaceutical turned 5 years in the market. Here, we

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set out to explore this unchartered territory on a national scale by making use of the German NET-Registry, which our institutions are part of. This registry has been described and analyzed in the past with data collection cutoff in 2010.[30] In view of this, the current retrospective study sheds new light on the German population with data collected until 2023 and allows for updated country-to-country comparisons where differences in demographics, diagnostics and therapeutics may be seen. The preliminary results of this exploratory data-driven analysis are described in this document.

2. Methods

2.1. Database

This retrospective study is based on data extracted from the German NET-Registry, a nation-wide survey collecting pseudomyzed NEN cases from medical centers all over Germany. The study is of exploratory nature. The registry is organized by the German Society of Endocrinology and the general mode of operation has been previously described.[31] Briefly, after registering at the NET-Registry, the participating centers (private clinics, teaching, community and regional hospitals) must receive approval from the local ethics committees. Additionally, approval from the Institutional Review Board at Charité Mitte (Berlin, Germany) is obtained. Before recording patient data into the registry, signed informed consent must be obtained from the NEN patients. In addition to signed informed consent, patients need to have a histologically confirmed NEN diagnosis and be ≥ 18 years old. To note, in this retrospective study only NENs of GEP origin were included and only patients receiving antitumoral therapy with at least PRRT being one of them were included (further study entry criteria are listed in section 2.2). These patients were scheduled for follow-up visits during treatment (at intervals between doses) and in post-treatment (every 3-6 months, then annually).

Data collection and reporting into the registry was conducted by the center personnel using a standardized questionnaire designed by a panel of 11 specialists experienced in the care of patients with NENs. A minimum set of items was deemed mandatory including date of diagnosis, sex, age, among others. Some items might have been left unanswered if the required information from the patient was not available at the center-level (e.g., Ki-67 or WHO performance status scores) due to a lost to follow-up case, undisclosed information, assessment not done, or any other reason. The center personnel were requested to input data using the patient medical records as source to prevent any memory bias. Following the data submission, further checks and validations were conducted to identify any unusual values, which were then addressed with the individual who submitted the data.

The database is considered representative as distribution data are similar to those documented in the published literature.[31] Further details including previous publications about the German NET-Registry can be found in the dedicated website of the registry (www.net-register.org).

2.2. Patient selection

The data extract used in this study contains consenting patients diagnosed with a GEP-NEN who sought medical attention at one of the NET-Registry's affiliated centers and received PRRT. Patients on ^{177}Lu-based PRRT were assigned a standard schedule of approximately 7.4 GBq per cycle, given every 8 weeks for a total of 4 cycles. Patients on ^{90}Y-based PRRT were assigned a standard schedule of about 3.7 to 4.4 GBq per cycle, given every 8 weeks for a total of 2 to 4 cycles. Modifications to the schedule and dose were at the physician's discretion based on the patient's response or tolerance. Surveys of all patients with a first diagnosis from 1995 to 2023 were available from 22 centers across Germany. The inclusion and exclusion criteria that were used in this study are listed below. All participants must satisfy all the criteria.

Inclusion criteria: male or female patients ≥ 18 years old at the time of study inclusion; diagnosis of GEP-NEN between 1995 to 2023 and receiving PRRT within this period; patients who, in the opinion of the investigator, can and will comply with the requirements of the study procedures; and patients who are able to provide written informed consent, or otherwise written informed consent from their caregivers.

Exclusion criteria: patients without a confirmed histological diagnosis of GEP-NEN; incomplete medical records or inability to confirm key inclusion data points; and patients who are unwilling or unable to participate in required follow-up visits, surveys, or tests.

2.3. Study variables

The study variables included patients age and sex, site of primary tumor, WHO 2019 grading (for consistency purposes, tumors originally classified using previous WHO criteria versions were re-classified into the 2019 WHO version when data about Ki-67 and differentiation were available; histopathology reports were reviewed.),[2] presence of metastasis, Ki-67, WHO performance status scores,[32] and diagnosis of cancer of unknown primary (CUP) (all these determined at first diagnosis of the GEP-NEN, except site of primary tumor which could have been determined after initial diagnosis of CUP). Further study variables included sites of metastasis, therapy lines and type of therapy, and tumor response after last intervention (all these determined from the moment of patient inclusion into the registry and throughout the follow-ups). Routine histology reports and reference pathology reports were used as available. As Ki-67 determination for grading is standard of care, grading based on Ki-67 determination is documented within the registry.

Data about the following therapy types were collected: surgery, locoregional therapy, PRRT (including ^{177}Lu-coupled and others), radiotherapy and pharmacological therapy (chemotherapy, IFN-alpha, MTT including everolimus and sunitinib, and SSA). Second-line therapy (or any subsequent one) is typically defined as any therapy administered for disease progression, recurrence, or intolerable adverse effects following administration of initial therapy.

The study population was characterized using general epidemiological information and disease-specific information derived from the study variables mentioned above. Given the advances in medicine and access to healthcare in the past 2 decades, the treatment-specific information was only analyzed in an open patient cohort consisting of a sample of those with a first diagnosis from 2010 to 2023, which will be referred to as the "therapy cohort."

2.4. Imaging and tumor response to treatment

Target lesions were measured and classified on SSR imaging and anatomical imaging, at baseline and within 6 months after each intervention (accepted range 1–6 months). Radiology reports were used to determine the tumor response. Patients were also examined for the presence of new metastases during these follow-ups. Whenever tumor response data after last intervention was not available, it was assumed to be progressive if patient was found to have expired within the follow-up period due to NEN-related causes.

2.5. Time to strategy failure

Time to strategy failure (TSF) is defined as measuring time from start of PRRT to start of the next therapy line, progression of

disease, or death, whichever occurred first. Median TSF and interquartile ranges were calculated.

2.6. Statistical analysis

Descriptive statistics were used to summarize the data. Graphs and statistical analyses were performed with Microsoft Excel (Microsoft, Redmond), SPSS Statistics (IBM, Armonk), GraphPad QuickCalcs (Dotmatics, Boston), Plotly.js (Plotly, Inc, Montreal [Quebec], Canada) and Tableau Public (Salesforce, San Francisco), with use of standard two-tailed unpaired Student *t* test for normally distributed data, otherwise Kruskal–Walis test. Normal distribution was tested by Shapiro–Wilk W test with an alpha level of .05. *P* values lower than .05 were considered statistically significant. In case of missing datapoints, the number of unknowns was duly reported or otherwise statistics were performed on the number of non-missing datapoints only.

3. Results

3.1. Patient clinical characteristics

The study initially included a total population of 231 patients diagnosed with GEP-NENs who received at least one PRRT. 28 patients meeting the criteria mentioned before were excluded from the study due to substantial amounts of data missing (e.g., details on histology and demographics), resulting in 203 patients passing all inclusion and exclusion criteria The mean age of the total population at diagnosis was 58 years (SD 12 years), with a minimum of 25 and a maximum of 84 years. 98 (48.3%) of patients were female and 108 (51.7%) were male. Mean follow-up period was 6.9 years (0.4–33.2; SD 5.5). WHO performance status was documented for 99 patients. The majority had a WHO performance status score of 1 or 0 (50.5% and 41.4%, respectively), while 6 patients had a score of 2 (61%), score 3 was only observed in one patient (10%) and score 4 was also only observed in one patient (1.0%). Notably, scores 3 and 4 were G1 and G2 pNET patients (Table 1). A statistical test to determine whether one sex is more prone to be diagnosed with GEP-NEN earlier and therefore assumed to develop the disease earlier revealed no significance (*P* = .70) (Fig. 1).

Clinical characteristics were also assessed in the therapy study cohort. This cohort included 98 patients. The mean age of the cohort at diagnosis was 59 years (SD 12 years), with a minimum of 25 and a maximum of 84 years. 48 (49.0%) of patients were female and 50 (51.0%) were male. Mean follow-up period was 4.4 years (0.4–13.3; SD 2.7). WHO performance status was documented for 72 patients. The majority of patients had a WHO performance status score of 0 or 1 (40.3% and 51.4%, respectively), while 4 patients had a score of 2 (5.6%), score 3 was only observed in one patient (1.4%) and score 4 was also only observed in 1 patient (1.4%). Notably, scores 3 and 4 were the same patients identified above as diagnosed with pNET (Table 2). A statistical test to determine whether one sex is more prone to be diagnosed with GEP-NEN earlier and therefore assumed to develop the disease earlier revealed no significance (*P* = .83) (Fig. 2).

Table 1

Clinicohistopathological characteristics of the total study population (1995–2023).

Variable	Total number of patients (%)
n	203 (100.0)
Age at Dx	
Mean age (years), (SD)	58 (12)
Median age (years), (range)	59 (25-84)
Mode age (years) = 67	12 (5.9)
Age group	
18–30	3 (1.5)
31–40	14 (6.9)
41–50	35 (17.2)
51–60	55 (27.1)
61–70	65 (32.0)
71–80	29 (14.3)
>80	2 (1.0)
Women	95 (48.3)
Men	108 (51.7)
WHO classification at Dx	
(documented for n = 170)	
NET, G1	58 (34.1)
NET, G2	94 (55.3)
NET, G3	8 (4.7)
NEC	10 (5.9)
Site of primary tumor	
Stomach	3 (1.5)
Pancreas	94 (46.3)
Small intestine	92 (45.3)
Caecum	4 (2.0)
Colon	4 (2.0)
Rectum	6 (3.0)
WHO performance status at Dx	
(documented for n = 99)	
0	41 (41.4)
1	50 (50.5)
2	6 (6.1)
3	1 (1.0)
4	1 (1.0)
Metastasis at Dx	
Yes	150 (74.0)
No	16 (7.9)
Unknown	37 (18.2)
Site of metastases (n = 163 in	
stage IV)	
Bones	67 (41.1)
Cerebral	4 (2.5)
Liver	156 (95.7)
Lung	15 (9.2)
Lymp nodes	73 (44.8)
Other	32 (19.6)
Peritoneum	25 (15.3)
Ki-67 (documented for	
n = 183)	
<3%	58 (31.7)
3–20%	106 (57.9)
>20%	19 (10.4)
CUP at Dx	
Yes	32 (15.8)
No	171 (84.2)

CUP = cancer of unknown primary, Dx = diagnosis, G1, G2, G3 = grade 1, 2 and 3, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, SD = standard deviation, WHO = World Health Organization.

3.2. Disease-specific characteristics

The majority of GEP-NEN patients presented stage IV disease at diagnosis (73.9%), with liver metastasis being the most common (present in 95.7% of stage IV patients). A minority of patients were diagnosed with CUP (15.8%). However, it should be noted that physicians were then able to determine the primary tumor of all of these patients, as confirming a diagnosis of GEP-NEN was necessary for study inclusion. Pancreas and small intestine were the most common primary tumor sites in the population (46.3% and 45.3%, respectively). In terms of sex, pancreatic NENs (pNENs) were slightly more often found in male than in female patients (55/94 pNEN patients were men). WHO grading was documented for 170 patients. In this subgroup, primary tumors were classified most often as WHO G2 and G1 GEP-NETs (55.3% and 34.1%, respectively), while 8 patients (4.7%) were found to have G3 GEP-NETs and 10 (5.9%) were found to have GEP-NECs. Further subclassification into small and

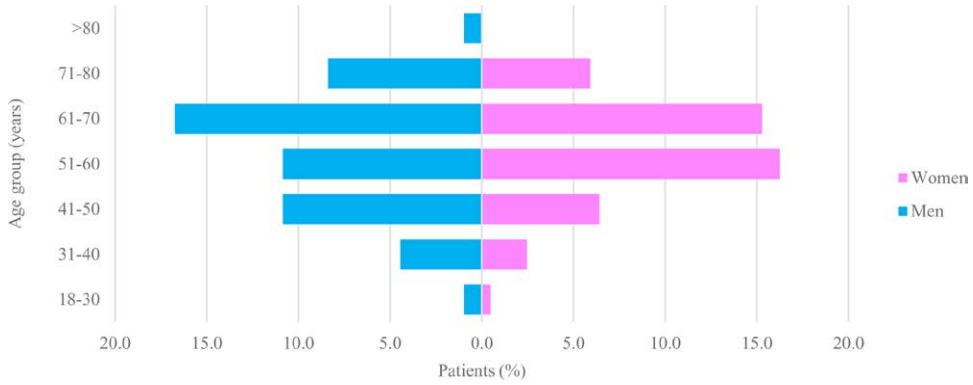

Figure 1. Distribution of study population by age and sex (1995–2023). n = 203 patients diagnosed with GEP-NEN. No significant difference was found between the ages of men and women (*P* value = .70). The mean of men minus women = −0.65. 95% confidence interval of this difference: from −4.02 to 2.71. GEP-NEN = gastroenteropancreatic-neuroendocrine neoplasia.

large-cell type NEC was not possible due to lack of data. Full disease-specific data with absolute numbers and percentages are shown in Table 1.

Disease-specific characteristics were also assessed in the therapy study cohort. Here, similar trends were observed as with the total study population. 91.8% of cohort patients presented metastasis at diagnosis and 98.0% presented metastasis at diagnosis or at the follow-ups. The small intestine and pancreas were the most frequent primary tumor sites (51.0% and 43.9%, respectively). In terms of sex, pNENs were slightly more often found in men than in women (26/43 pNEN patients were men). The majority of patients were found to have G2 and G1 GEP-NETs (48.8% and 39.0%, respectively), while 5 patients (6.1%) were classified with G3 GEP-NET and 5 patients (6.1%) were classified with GEP-NEC. Full disease-specific data with absolute numbers and percentages about the therapy cohort is shown in Table 2.

3.3. Therapies

Therapies were analyzed based on type, occurrence and sequence (therapy-lines). This information is expected to offer additional understanding on the quality and cost of care for GEP-NET patients.

Table 3 shows the overall rate of therapies in the therapy cohort of the study (n = 98), from first-line therapy to fourth-line therapy. Of note, 17 patients (17.4%) were reported to continue with further lines of therapy after fourth line. In PRRT receiving patients, SSA and surgery were the most frequent therapies (65.3% and 60.2%, respectively) alongside PRRT. Among the pharmacological options, there was a higher occurrence of SSA and chemotherapy use than MTT or IFN-alpha (65.3% and 50.0% vs 16.3% and 2.0%, respectively). Additionally, 10.2% of patients received locoregional therapies and 7.1% were reported to go through radiotherapy sessions. PRRT was found to be mostly used as the formulation that includes radionuclide ^{177}Lu instead of ^{90}Y (95.9% vs 15.7%, respectively). 12 patients were reported to undergo at least one cycle with both forms of PRRT, most of which started PRRT with ^{90}Y and the next injection was with ^{177}Lu (data not shown).

The most common first-line therapy was surgery, as seen in 37 patients (37.8%), followed by SSA in 27 patients (27.6%). PRRT as a first-line therapy was found in 13 patients (13.3%). Among patients receiving subsequent-line therapies, PRRT was always found as the most common option (Table 4).

Table 5 shows the frequencies of therapy types before administration of PRRT, when PRRT was administered as a second-line therapy or a third-line therapy. Among the 34 patients receiving PRRT as a second-line therapy, 14 (41.2%) had surgery as a first-line therapy while 12 (35.3%) received SSA as a first-line therapy. Among the 30 patients receiving PRRT as a third-line therapy, the most common sequence of first and second-line treatments was surgery followed by SSA, as seen in 16 patients (53.3%).

3.4. Tumor response analysis and time to strategy failure

Tumor response after each intervention was assessed via imaging and analyzed in this study for the therapy cohort. Whenever tumor response data was not available, it was assumed to be progressive if a patient was found to have expired within the follow-up period due to NEN-related causes (this was the case for 12 patients), otherwise it was deemed unknown (Table 6). It was in the interest of the authors to examine the response after PRRT was administered as a first, second, third and fourth-line therapy. Average imaging follow-up period was 3.5 years (SD 2.69).

Most patients receiving PRRT as a first-line therapy were found to have stable disease at 6 months follow-up (7/12 patients or 58.3%). In patients receiving PRRT as a second-line therapy, clinical benefit (stable disease or remission) was observed in 21/35 patients (60.0%), while 4 patients (11.4%) were found to show progressive disease and 10 (28.6%) had an unknown response. Most patients who received PRRT as a third-line therapy had a fairly equal distribution between progressive disease (9/30 or 30.0%) and stable disease (10/30 or 33.3%). However, for a substantial number of patients in this subgroup the response was unknown (11/30 or 36.7%). Most patient receiving PRRT as a fourth-line therapy showed features of progressive disease (7/21 or 33.3%), however in this subgroup the number of unknown responses is also substantial (8/21 or 38.1%). These and further details are displayed in Table 6. Given the large number of unknown responses and the small number of patients, it was not possible to perform correlation statistics during this analysis.

To further compare the efficacy of PRRT intervention at different timepoints of a treatment sequence, we measured TSF (Fig. 3). The median TSF of the patients was 325.5 days (IQR: 172–958) with first-line PRRT, 376 days (IQR: 190.6–1228.5) with second-line PRRT, 276 days (IQR: 84–598) with third-line PRRT and 742.5 days with fourth-line PRRT (IQR: 172.5–1400). PRRT as a second-line therapy was shown to have the shortest median time to failure, indicating it may be less effective or have a quicker relapse compared to the others. Overall, this data revealed that on average patients stayed on PRRT, showed no signs of progression or fatal outcomes for 430 days. Remarkably, 37.1% of patient receiving second-line PRRT had no failure in strategy, i.e. no interruption of PRRT, progression or death, while in the other subgroups no failure of strategy was seen in less than 14%

Table 2

Clinicohistopathological characteristics of the therapy cohort (2010–2023).

Variable	Total number of patients (%)
n	98 (100.0)
Age at Dx	
Mean age (years), (SD)	59 (12)
Median age (years), (range)	61 (25–84)
Mode = 61	6 (6.1)
Age group	
18–30	2 (2.0)
31–40	5 (5.1)
41–50	15 (15.3)
51–60	26 (26.5)
61–70	28 (28.6)
71–80	20 (20.4)
>80	2 (2.0)
Women	48 (49.0)
Men	50 (50.0)
WHO classification at Dx (documented for n = 82)	
NET, G1	32 (39.0)
NET, G2	40 (48.8)
NET, G3	5 (6.1)
NEC	5 (6.1)
Site of primary tumor	
Stomach	1 (1.0)
Pancreas	43 (43.9)
Small intestine	50 (51.0)
Caecum	2 (2.0)
Colon	1 (1.0)
Rectum	1 (1.0)
WHO performance status at Dx (documented for n = 72)	
0	29 (40.3)
1	37 (51.4)
2	4 (5.6)
3	1 (1.4)
4	1 (1.4)
Metastasis at Dx	
Yes	90 (91.8)
No	6 (6.1)
Unknown	2 (2.0)
Site of metastases (n = 96 in stage IV)	
Bones	39 (40.6)
Cerebral	3 (3.1)
Liver	92 (95.8)
Lung	10 (10.4)
Lymp nodes	44 (45.8)
Other	16 (16.7)
Peritoneum	14 (14.6)
Ki-67 (documented for n = 93)	
<3%	32 (34.4)
3–20%	49 (52.7)
>20%	12 (12.9)
CUP	
Yes	23 (23.5)
No	75 (76.5)

CUP = cancer of unknown primary, Dx = diagnosis, G1, G2, G3 = grade 1, 2 and 3, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, SD = standard deviation, WHO = World Health Organization.

(data not shown). To note, the seemingly large median TSF of PRRT as a fourth-line therapy is opposed to the previous revelation that progressive disease was most often seen within 6 months after receiving fourth-line PRRT. This is explained by the fact that many of the tumor responses within 6 months of PRRT in this subgroup are unknown, however radiology reports of later follow-ups were made available, and these skewed the TSF towards longer times. Importantly, the data from this analysis failed to achieve statistically significant differences (P value = .49).

Table 3

Frequency of other therapies at any time during the observation period in the therapy cohort (2010–2023).

Variable	Total number of patients (%)
n	98 (100.0)
Therapy	
Surgery	59 (60.2)
Radiotherapy	7 (7.1)
Chemotherapy	49 (50.0)
SSA	64 (65.3)
IFN-alpha	2 (2.0)
MTT	16 (16.3)
Locoregional therapy	10 (10.2)

IFN-alpha = interferon alpha, MTT = moleculary targeted therapy (sunitinib, everolimus), SSA = somatostatin analog.

4. Discussion

Diagnoses of GEP-NENs are on the rise on a worldwide scale. Better access to healthcare resources, and particularly the increased availability of proper diagnostic tools, are considered to contribute to these rising figures.[3] PRRT is an increasingly used therapy option entering the field of GEP-NEN disease management. First developed in Europe in the early 1990s and used on selected patients even before approval through compassionate use programs, PRRT with ^{177}Lu-DOTATATE received approval from the EMA in 2017 with an indication for adults with SSR-expressing progressive advanced GEP-NENs.[21,33] In the present study, we demonstrate real-world evidence of clinical and histopathological characteristics of patients diagnosed with GEP-NENs in Germany, including treatment patterns, from 1995 to 2023, who received PRRT among other therapies. Patient data was retrieved from the German NET-Registry, the first national registry collecting real-world data on NENs across Germany.[31] The data should be representative, as they have been contributed by centers of different sizes. As mentioned previously, certain GEP-NEN entities are likely to become underrepresented given that local practices show they are rarely referred to any NET centers (e.g., appendiceal NENs, type I gastric NENs, and small rectal NENs including incidental findings).[34]

Kasajima et al stated in 2022 that data on high-grade neuroendocrine neoplasia including NET G3 and NEC was still scarce.[35] The present study includes data about low-grade and high-grade NETs, as well as NECs, which should serve the purpose of better understanding NEN disease by filling the data gap previously mentioned.

The clinical characteristics of the total patient population such as age, gender ratio, WHO performance status and cancer stage are consistent with previous findings concerning GEP-NEN patients in other European countries[16,36] and larger studies.[25] Our results show that there is a fairly equal distribution of gastrointestinal tract NENs versus pNENs. This has been previously observed by other authors.[37] Furthermore, almost 3 quarter (73.9%) of patients are diagnosed with stage IV disease. Unfortunately, this is quite common in clinical practice, as most NENs are nonfunctional and patients tend to be initially diagnosed with an incorrect histopathology.[9] The widespread use of modern immunohistochemical techniques should serve to circumvent this issue, however it should be noted that patients presenting nonspecific symptoms might not be considered for referral to NET centers and therefore an underrepresentation of early stage GEP-NENs may be occurring in the registry. The lack of severe symptomatology would also explain the low WHO performance status at diagnosis in spite of the initial presence of metastasis. The finding of one pNET patient with WHO score 4 at first diagnosis who then underwent PRRT represents a rarity in the sense that bedbound patients are usually not eligible for

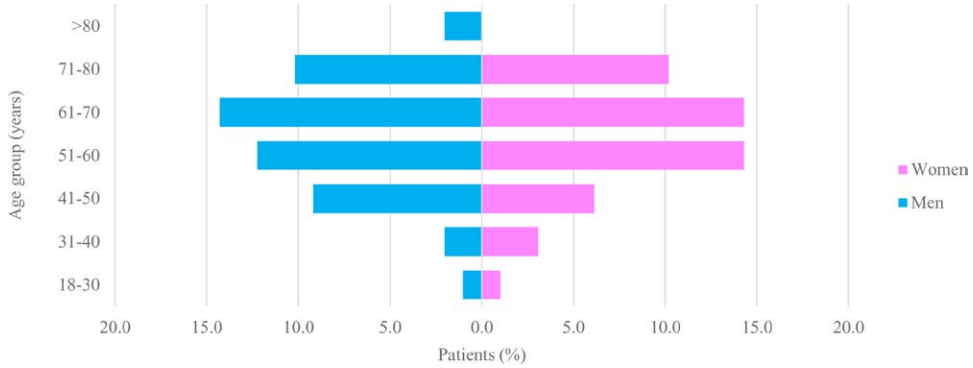

Figure 2. Distribution of the therapy cohort by age and sex (2010–2023). n = 98 patients diagnosed with GEP-NEN. No significant difference was found between the ages of men and women (*P* value = .83). The mean of men minus women = –0.55. 95% confidence interval of this difference: from –4.61 to 5.71. GEP-NEN = gastroenteropancreatic-neuroendocrine neoplasia.

Table 4

Lines of therapies in patients from the therapy cohort (2010–2023). The first observation (n) takes into account how many patients from the total 98-patient cohort received a first, second, third and fourth line of therapy. The second observation (n2) takes into account how many patients received each type of therapy, per therapy line. Of note, 17 patients were reported to continue with further lines of therapy after fourth-line.

Variable	Total number of patients (%)			
n	98 (100.0)			
Therapy line	1st line	2nd line	3rd line	4th line
Any therapy	98 (100.0)	93 (98.9)	71 (72.5)	43 (43.9)
Variable per therapy line	**1st line**	**2nd line**	**3rd line**	**4th line**
n2	98 (100.0)	93 (100.0)	71 (100.0)	43 (100.0)
Surgery	37 (37.8)	9 (9.7)	7 (9.9)	6 (14.0)
Radiotherapy	0 (0.0)	0 (0.0)	4 (5.6)	3 (7.0)
Chemotherapy	20 (20.4)	15 (16.1)	10 (14.0)	4 (9.3)
SSA	27 (27.6)	27 (29.0)	9 (12.7)	1 (2.3)
IFN-alpha	0 (0.0)	1 (1.1)	0 (0.0)	1 (2.3)
MTT	1 (1.0)	4 (4.3)	7 (9.9)	4 (9.3)
Locoregional therapy	0 (0.0)	3 (3.2)	4 (5.6)	3 (7.0)
PRRT*	13 (13.3)	34 (36.6)	30 (42.3)	21 (48.8)

IFN-alpha = interferon alpha, MTT = moleculary targeted therapy (sunitinib, everolimus), PRRT = peptide receptor radionuclide therapy, SSA = somatostatin analog.

* PRRT cycles with radionuclides ^{177}Lu or ^{90}Y. 95.92% of PRRT-receiving patients used the formulation with ^{177}Lu; 15.68% of PRRT-receiving patients used the formulation with ^{90}Y.

PRRT. We cannot exclude the possibility of a data entry error rather than a clinical exception. We do not show functionality data as this was not available for most patients in the study. This issue has been previously highlighted as a finding from the German NET-Registry and probably derives from an error in documentation practices from the participating centers.[3] A minority of patients presented with CUP at diagnosis (15.8% of the total study population and 23.5% of the therapy cohort) and all primary tumors were discovered in later follow-ups, which made them eligible for this study. However, outside this registry, despite numerous advances in diagnostics, it is estimated that the primary tumor site remains unknown in around 11% to 22% of NEN cases.[38]

Given the current emphasis on sex/gender-specific medicine[39] and evidence of longer overall survival in women with GEP-NEN,[40] we were interested to check for any sex-related differences in our study population. No sex quotas were used for this study. Patients passing eligibility criteria resulted in a fairly equal percentage of men and women, both in the total study population (51.7% and 48.3%, respectively) and in the therapy cohort (51.0% and 48.9%, respectively). Primary tumor distribution was slightly more inclined towards men to have pNEN than women both in the total study population (58.5% of pNEN patients were men) and in the therapy cohort (60.5% of pNEN patients were men). This could be one of the reasons why women have been found to exhibit longer overall survival in other studies, as pNENs tend to have the worst prognosis.[1] No statistical significance was found when determining whether one sex is more prone to develop the disease at an earlier age than the other. Some other recent studies to elucidate sex-based clinicopathological differences as well as outcomes among patients with GEP-NEN in Europe have been recently carried out and coincidentally found no relevant significant differences based on sex.[41,42]

Prognosis of GEP-NEN is heavily determined by histopathology,[43] which explains the importance of not only staging but Ki-67 and WHO classification. Given that all patients included in this study received PRRT, it was expected to find WHO grades typically associated with high SSR expression. However, there is a small minority of GEP-NET G3 patients found among the study population (4.7%). Careful examination of source documents of each of these 8 cases revealed that 3 patients were diagnosed between 2004 and 2009, and 5 were diagnosed in 2010 or more recently, which should minimize the error of misclassification given that no diagnoses were performed before the year 2000. Additionally, the 8 patients come from 3 different centers, which annuls the possibility of this issue being a unique center characteristic. Seven of these patients had a NEN of pancreatic

origin, which is the most common origin of G3 NETs according to the WHO.[2] Notably, 6 G3 GEP-NET patients either had the primary tumor detected via SSR-based imaging, or imaging follow-ups were performed with SSR-based imaging (SSR scintigraphy, PET or combined tomography). One case involved a pancreatic tumor first diagnosed as poorly differentiated endocrine carcinoma (PDEC) according to WHO 2000 classification with Ki-67 = 25%, which years later was re-classified as G3 NET. While not a typical characteristic of G3 NETs, there have been prior cases reported in the literature of patients with G3 NETs exhibiting a positive SSR imaging uptake and receiving PRRT.[44,45] 2 of these G3 NET patients were treated with ^{177}Lu-DOTATATE after EMA approval, which would indicate clinician's decision to use PRRT off-label or for investigational purposes as done in the NETTER-2 trial.[18]

As mentioned previously, treatment patterns and outcomes were analyzed in the therapy cohort (2010–2023). The occurrences of each therapy option are in line with pan-European NEN patient studies.[37] The 2 most common first-line therapies in our study were surgery and SSA, which follows the same trend observed in a recent study in Sweden[16] as well as the trend observed in the German NET-Registry up to 2010.[30] This trend is aligned with the therapies of choice as recommended by ESMO.[1] Radiotherapy and IFN-alpha were the 2 least frequent therapies observed in our study. Radiotherapy is usually administered in the form of palliative treatment of bone metastasis.[46] Accordingly, the radiotherapy-receiving patients in our study presented with bone metastasis. IFN-alpha, probably due to its side effects, was administered only to 2 patients in the therapy cohort, after use of SSA in a prior therapy line. This modality would follow the established approach of administering IFN-alpha in second-line as an add-on treatment to SSA in patients with refractory syndrome,[47] or when other therapeutical options have been exhausted or are not appropriate, particularly in midgut NETs where therapeutical options are more limited in contrast to those for pNETs.[1] Of note, both patients had iliac NEN, one G1 and one G2, and were treated in different centers. No information on presence of refractory carcinoid syndrome was made available.

All patients in our study received PRRT, as required per study inclusion criteria, however the complexity in treating GEP-NEN patients is observed in the several, different combinations of treatment lines and therapy options besides PRRT cycles. The therapy cohort revealed that most patients required surgical resection (37.8%) as a first-line therapy, however most patients from this subgroup required further treatment in the sense of biological therapy (e.g., SSAs) in addition to cycles of PRRT. PRRT as a second or third-line therapy is common in clinical practice as the recommendation is to consider it after failure of other therapies.[48] Of note, not all surgeries prior to PRRT should be considered as failed attempts at curing, as currently there is an interest in using surgery before PRRT to remove bulky lesions which are unlikely to result in shrinkage from the therapy. To that effect, a phase IV clinical trial is currently ongoing (clinicaltrials.gov identifier: NCT06016855). PRRT as first-line therapy in our study was the least frequent option, coming after surgery and pharmacological therapy. This was expected due to the clinical practice recommendations, however it should be noted there is current interest in considering PRRT as a first-line therapy, including clinical trials.[1,18,49] Of note, this analysis on therapy lines does not discriminate between curative, adjuvant, neoadjuvant or palliative therapies. This is because in a retrospective study it is difficult to confirm the purpose of each therapy, as the possibility of contacting each treating physician does not exist. Nonetheless, this analysis should provide an updated snapshot of the quality of GEP-NEN patients and could trigger future cost of care research.

It should be noted that one of the aims of this study was not to evaluate overall or long-term patient survival but rather tumor response within 6 months after PRRT. This provides an idea about the short-term progression-free survival time, particularly important for PRRT as it has been recommended as an alternative when patients respond with progression while on other agents. We observed PRRT being administered either as a first, second, third or fourth-line therapy. Tumor response based on radiology reports revealed a result of mostly stable disease when PRRT was applied as a first, second or third-line therapy. Unfortunately, the large number of unavailable follow-up imaging data does not allow for statistical correlation analysis or time to progression/remission analysis. Additionally, analyzing response based on Chromogranin-A levels could not be performed for the

Table 5

Frequencies of therapies before peptide receptor radionuclide therapy in the therapy cohort (2010–2023).

	Total number of patients (%)
Second-line: PRRT	**34 (100.0)**
First-line:	
Surgery	14 (41.2)
Radiotherapy	0 (0.0)
Chemotherapy	8 (23.5)
SSA	12 (35.3)
IFN-alpha	0 (0.0)
MTT	0 (0.0)
Locoregional therapy	0 (0.0)
Third-line: PRRT	**30 (100.0)**
First and second-line sequences:	
Surgery and SSA	16 (53.3)
Sugery and chemotherapy	1 (3.3)
SSA and surgery	5 (16.7)
Chemotherapy and chemotherapy*	3 (10.0)
SSA and MTT	3 (10.0)
SSA and locoregional therapy	2 (6.7)

IFN-alpha = interferon alpha, MTT = moleculary targeted therapy (sunitinib, everolimus), PRRT = peptide receptor radionuclide therapy, SSA = somatostatin analog.

* Sequence of 2 different chemotherapies not part of the same therapy line.

Table 6

Response rate by peptide receptor radionuclide therapy according to line of therapy. Data is represented as n (% of patients in the line of therapy). No complete remissions or recurrences were observed. Average imaging follow-up period was 3.5 years (SD 2.69).

PRRT line of therapy	Patients treated	Progressive disease*	Stable disease	Partial remission	Unknown
1st	12	2 (16.7%)	7 (58.3%)	1 (8.3%)	2 (16.7%)
2nd	35	4 (11.4%)	16 (45.7%)	5 (14.3%)	10 (28.6%)
3rd	30	9 (30.0%)	10 (33.3%)	0 (0.0%)	11 (36.7%)
4th	21	7 (33.3%)	4 (19.0%)	2 (9.5%)	8 (38.1%)

PRRT = peptide receptor radionuclide therapy.

* Whenever tumor response data was not available, it was assumed to be progressive if patient was found to have expired within the follow-up period due to NEN-related causes. This was the case for 12 patients.

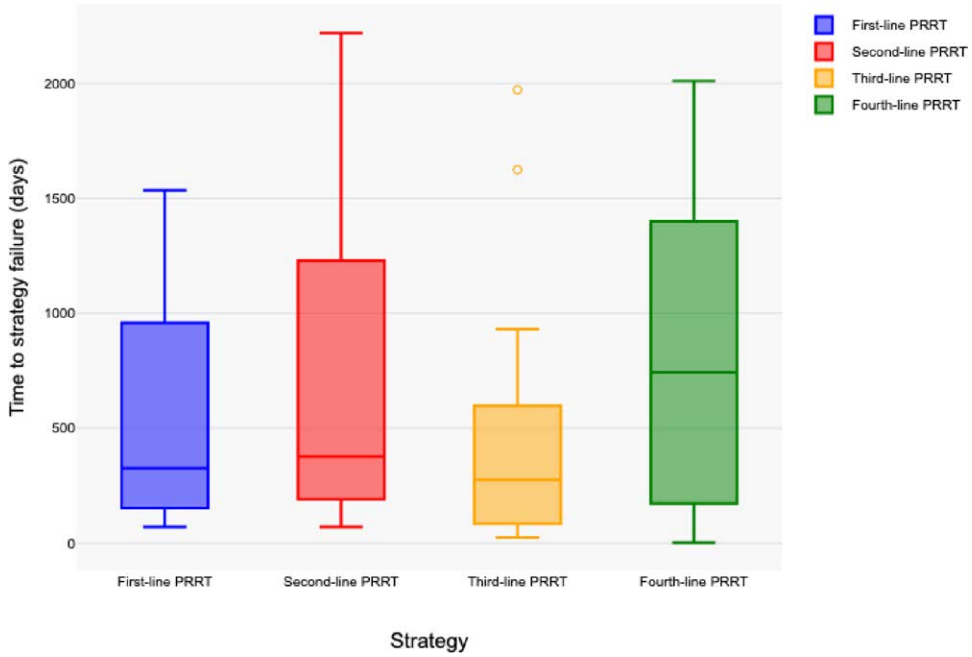

Figure 3. Boxplot showing the time to failure of strategy of peptide receptor radionuclide therapy in the therapy cohort (2010–2023), according to line of therapy. Median time to strategy failure is illustrated. First-line PRRT: 325.5 days (IQR: 172–958); second-line PRRT: 376 days (IQR: 190.6–1228.5); third-line PRRT: 276 days (IQR: 84–598); fourth-line PRRT: 742.5 (IQR: 172.5–1400). No significant difference was found between the groups (P = .49). IQR = interquartile range, PRRT = peptide receptor radionuclide therapy.

same reason. While most therapeutical protocols for NEN recommend follow-up scans every 6 months or, particularly for PRRT, cross-sectional imaging 2-3 and 6 months after the last cycle, this may not always be feasible in real-world clinical practice.[47,50] Lost to follow-up cases should also be accounted for the missing data. Hence, this study is based on documented clinical observations, and the various forms of progression following PRRT reported in this study may necessitate additional investigations. Notably, RECIST 1.1 criteria do not take into account the phenomenon of pseudo-progression in response evaluation. Use of RECIST 1.1 in the presence of pseudo-progression is a possible confounder. Pseudo-progression should be considered when there is an increase in tumor size observed during or after undergoing PRRT.[51] This phenomenon, first observed in gliomas treated with temozolomide combined with radiotherapy, and now largely associated with cancer immunotherapy, likely stems from radiogenic edema and inflammation, and does not accurately reflect the tumor's response to the therapy.[52,53] Functional imaging, such as PET/CT, can aid in distinguishing between genuine progression and pseudo-progression when the latter is suspected.[54] Given the retrospective nature of this study, there was no control on the choice of imaging technology used by the physicians in the participating centers.

To the best of our knowledge, there has been no report on TSF, progression-free survival or overall survival with regards to PRRT used in four-line treatment sequences. TSF has been proposed as a surrogate endpoint for overall survival in other cancers where multiple drugs are also used sequentially, such as non small-cell lung cancer and colon cancer.[55,56] As this retrospective study did not involve long-term follow up of patients with any kind of therapy but rather the PRRT cycles, emphasis was placed on PRRT TSF. Nevertheless, the patient numbers studied here were insufficient to achieve enough statistical power. Additionally, the large number of unavailable data resulted in much variability.

It is the opinion of the authors that this study reveals the landscape of NEN disease and care in Germany with focus on patients receiving PRRT among other therapies. The results can be applied to bigger-scale epidemiological, pharmacoepidemiologic and health economics research. Additionally, we plan on continuing this exploratory, retrospective study to extend it beyond the data extract and harness the database's full potential. The heterogeneity in treatment patterns that are described in this document speaks about the different efforts currently pursued by healthcare providers in managing this difficult and rare disease. Given how frequent patients are diagnosed at an advanced stage, and that most cases are not part of familial syndromes, we recommend conducting research to find out markers predisposing individuals to developing NEN. This would allow for the implementation of routine screening practices in risk groups. Finally, and echoing the words of the ESMO Clinical Practice Guidelines for GEP-NEN,[1] we recommend conducting research to determine definite predictive markers. Meanwhile, we strongly advise following a personalized medicine approach based on a multidisciplinary board decision, individual patient characteristics, histopathological characteristics (including molecular profiling), as well as SSR imaging.

The current study has limitations. The foremost limitation is the retrospective nature of the study which is based on registry data sourced from different centers. Other limitations include the relatively small sample size, which is explained by the rarity of NENs, and this sample size is common for most other studies as clarified by Lesén et al, 2019.[16] Because this study encompasses cases from 1995 to 2023, the possibility of bias resulting from recent diagnostic developments as well as changing WHO classifications throughout the years cannot be excluded. Particularly, older cases had to be reevaluated in terms of histopathology using the WHO 2019 classification for consistency. This limitation explains why it was decided to have different cohorts. Patients with localized disease stages which are not typically referred to oncologists could be missing in the registry and thus could have been missed in this study. However, little or no impact is expected in the study results as PRRT is typically used for GEP-NENs with metastasis. The range of time between follow-up scans was variable, which could have affected the tumor response results. In addition, limited overall follow-up duration and the choice of PRRT (^{177}Lu or ^{90}Y-based) could have influenced the results of the TSF analysis. RECIST 1.1 criteria, when used by physicians, poses certain limitations applied to NENs, including confounding from pseudo-progression.[55]

Finally, absent variables such as genetic factors and socioeconomic status are to be noted. Nevertheless, this retrospective study presents a comprehensive and up-to-date characterization of registry data including treatment patterns that may serve as the foundation for future clinical research.

5. Conclusions

In summary, our data show that GEP-NENs are mostly diagnosed in stage IV. Surgery and SSA are the most common therapy options as part of the range of therapy lines in patients receiving PRRT. PRRT is still largely used as a subsequent line of therapy, i.e. not in a first-line setting. Such data contribute to an up-to-date picture of GEP-NEN (pharmaco)epidemiology in Germany and should spark new epidemiological, pharmacoepidemiologic and health economics research to advance the diagnostics and management of patients living with this disease.

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References

[1] Pavel M, Öberg K, Falconi M, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:844–60.
[2] Nagtegaal ID, Odze RD, Klimstra D, et al.; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182–8.
[3] Das S, Dasari A. Epidemiology, incidence, and prevalence of neuroendocrine neoplasms: are there global differences? Curr Oncol Rep. 2021;23:43.
[4] Grundmann N, Voigtländer S, Hakimhashemi A, Pape UF, Meyer M, Müller-Nordhorn J. Site-specific trends in gastroenteropancreatic neuroendocrine neoplasms in Bavaria, Germany. Cancer Med. 2023;12:19949–58.
[5] Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst. 2012;104:764–77.
[6] Díez M, Teulé A, Salazar R. Gastroenteropancreatic neuroendocrine tumors: diagnosis and treatment. Ann Gastroenterol. 2013;26:29–36.
[7] de Mestier L, Hentic O, Cros J, et al. Metachronous hormonal syndromes in patients with pancreatic neuroendocrine tumors: a case-series study. Ann Intern Med. 2015;162:682–9.
[8] Juhlin CC, Skoglund S, Juntti-Berggren L, Karlberg M, Calissendorff J. Non-functioning neuroendocrine pancreatic tumors transforming to malignant insulinomas – four cases and review of the literature. Neuro Endocrinol Lett. 2019;40:175–83.
[9] Basuroy R, Bouvier C, Ramage JK, Sissons M, Srirajaskanthan R. Delays and routes to diagnosis of neuroendocrine tumours. BMC Cancer. 2018;18:1122.
[10] Zheng C, Al Shabeeb R, Shah D, Sardana N. Slow and steady: a slowly progressing neuroendocrine tumor. ACG Case Rep J. 2023;10:e01147.
[11] Pape UF, Berndt U, Müller-Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer. 2008;15:1083–97.
[12] Arnold R, Wilke A, Rinke A, et al. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. Clin Gastroenterol Hepatol. 2008;6:820–7.
[13] Bergestuen DS, Aabakken L, Holm K, Vatn M, Thiis-Evensen E. Small intestinal neuroendocrine tumors: prognostic factors and survival. Scand J Gastroenterol. 2009;44:1084–91.
[14] Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
[15] Ter-Minassian M, Chan JA, Hooshmand SM, et al. Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database. Endocr Relat Cancer. 2013;20:187–96.
[16] Lesén E, Granfeldt D, Berthon A, et al. Treatment patterns and survival among patients with metastatic gastroenteropancreatic neuroendocrine tumours in Sweden – a population-based register-linkage and medical chart review study. J Cancer. 2019;10:6876–87.
[17] Sorbye H, Grande E, Pavel M, et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for digestive neuroendocrine carcinoma. J Neuroendocrinol. 2023;35:e13249.
[18] Simron S, Halperin DM, Myrehaug S, et al. [177Lu]Lu-DOTA-TATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors: primary analysis of the phase 3 randomized NETTER-2 study. JCO. 2024;42(3_suppl):LBA588.
[19] Bombardieri E, Seregni E, Evangelista L, Chiesa C, Chiti A. Clinical Applications of Nuclear Medicine Targeted Therapy, 1st ed. Springer; 2018.
[20] U.S. Food and Drug Administration. FDA approves lutetium Lu 177 dotatate for pediatric patients 12 years. Updated: April 23, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lutetium-lu-177-dotatate-pediatric-patients-12-years-and-older-gep-nets. Accessed May 26, 2024.
[21] Ichikawa Y, Kobayashi N, Takano S, Kato I, Endo K, Inoue T. Neuroendocrine tumor theranostics. Cancer Sci. 2022;113:1930–8.
[22] Cox T, O'Connell M, Leeuwenkamp O, Palimaka S, Reed N. Real-world comparison of healthcare resource utilization and costs of [177Lu]Lu-DOTA-TATE in patients with progressive neuroendocrine tumors in England: a matched cohort analysis using data from the hospital episode statistics dataset. Curr Med Res Opin. 2022;38:1305–17.
[23] Ramim JE, Matheos de Lima BA, Bulzico DA, Pujatti PB, Bergmann A. Prospective cohort real-world study on neuroendocrine tumor patient's quality of life during peptide receptor radionuclide therapy with 177Lu-DOTATATE. Pancreas. 2022;51:784–9.
[24] Jalbert JJ, Casciano R, Meng J, et al. Treatment patterns and health resource use among patients with metastatic gastroenteropancreatic

neuroendocrine tumors treated at a Tertiary Referral Center. Oncologist. 2020;25:e644–50.
[25] Loosen SH, Kostev K, Eschrich J, et al. Clinical characteristics of 662 patients with pancreatic neuroendocrine tumors receiving antitumoral therapy. Medicine (Baltimore). 2022;101:e32044.
[26] Smith D, Lepage C, Vicaut E, et al. Observational study in a real-world setting of targeted therapy in the systemic treatment of progressive unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors (pNETs) in France: OPALINE study. Adv Ther. 2022;39:2731–48.
[27] Hentzen S, Mehta K, Al-Rajabi RMT, et al. Real world outcomes in patients with neuroendocrine tumor receiving peptide receptor radionucleotide therapy. Explor Target Antitumor Ther. 2023;4:396–405.
[28] Baum RP, Wang P, Jakobsson V, et al. Peptide receptor radionuclide therapy (PRRT) in metastatic neuroendocrine tumors of unknown primary (CUP-NETs). Theranostics. 2024;14:133–42.
[29] Unal C, Alan Selcuk N, Biricik FS, et al. Assessing the clinical impact of Lutetium-177 DOTATATE peptide receptor radionuclide therapy (PRRT) on metastatic neuroendocrine tumors: a multicenter real-world data from Türkiye. EJMO. 2023;7:232–42.
[30] Begum N, Maasberg S, Plöckinger U, et al.; Weitere Vertreter des deutschen NET-Registers. Neuroendokrine Tumoren des Verdauungstrakts – Daten des deutschen NET-Registers [Neuroendocrine tumours of the GI tract – data from the German NET Registry]. Zentralbl Chir. 2014;139:276–83.
[31] Ploeckinger U, Kloeppel G, Wiedenmann B, Lohmann R; Representatives of 21 German NET Centers. The German NET-registry: an audit on the diagnosis and therapy of neuroendocrine tumors. Neuroendocrinology. 2009;90:349–63.
[32] Picot J, Cooper K, Bryant J, Clegg AJ. The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation. Health Technol Assess. 2011;15:1–204.
[33] Das S, Dasari A. Novel therapeutics for patients with well-differentiated gastroenteropancreatic neuroendocrine tumors. Ther Adv Med Oncol. 2021;13:17588359211018047.
[34] Begum N, Maasberg S, Pascher A, et al.; German NET-Registry. Long-term outcome of surgical resection in patients with gastroenteropancreatic neuroendocrine neoplasia: results from a German nation-wide multi-centric registry. Langenbecks Arch Surg. 2020;405:145–54.
[35] Kasajima A, Konukiewitz B, Schlitter AM, Weichert W, Klöppel G. An analysis of 130 neuroendocrine tumors G3 regarding prevalence, origin, metastasis, and diagnostic features. Virchows Arch. 2022;480:359–68.
[36] Popa O, Taban SM, Pantea S, et al. The new WHO classification of gastrointestinal neuroendocrine tumors and immunohistochemical expression of somatostatin receptor 2 and 5. Exp Ther Med. 2021;22:1179.
[37] Borbath I, Garcia-Carbonero R, Bikmukhametov D, et al. The European Neuroendocrine Tumour Society registry, a tool to assess the prognosis of neuroendocrine neoplasms. Eur J Cancer. 2022;168:80–90.
[38] Alexandraki K, Angelousi A, Boutzios G, Kyriakopoulos G, Rontogianni D, Kaltsas G. Management of neuroendocrine tumors of unknown primary. Rev Endocr Metab Disord. 2017;18:423–31.
[39] Muscogiuri G, Barrea L, Feola T, et al.; NIKE (Neuroendocrine Tumors, Innovation inKnowledge and Education) Group. Pancreatic neuroendocrine neoplasms: does sex matter? Trends Endocrinol Metab. 2020;31:631–41.
[40] White BE, Russell B, Remmers S, et al. Sex differences in survival from neuroendocrine neoplasia in England 2012–2018: a retrospective, population-based study. Cancers (Basel). 2023;15:1863.
[41] Mogl MT, Dobrindt EM, Buschermöhle J, et al. Influence of gender on therapy and outcome of neuroendocrine tumors of gastroenteropancreatic origin: a single-center analysis. Visc Med. 2020;36:20–7.
[42] Jann H, Krieg S, Krieg A, et al. Analyses of sex-based clinicopathological differences among patients with gastrointestinal neuroendocrine neoplasms in Europe. J Cancer Res Clin Oncol. 2023;149:7557–63.
[43] Oberg K. Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors. Clinics (Sao Paulo). 2012;67(Suppl 1):109–12.
[44] Heetfeld M, Chougnet CN, Olsen IH, et al.; other Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2015;22:657–64.
[45] Graf A, Welch J, Bansal R, et al. Metastatic grade 3 neuroendocrine tumor in multiple endocrine neoplasia type 1 expressing somatostatin receptors. J Endocr Soc. 2022;6:bvac122.
[46] Guan M, He I, Luu M, et al. Palliative radiation therapy for bone metastases in neuroendocrine neoplasms. Adv Radiat Oncol. 2019;4:513–9.
[47] Tsoli M, Chatzellis E, Koumarianou A, Kolomodi D, Kaltsas G. Current best practice in the management of neuroendocrine tumors. Ther Adv Endocrinol Metab. 2018;10:2042018818804698.
[48] Merola E, Grana CM. Peptide Receptor Radionuclide Therapy (PRRT): innovations and improvements. Cancers (Basel). 2023;15:2975.
[49] Satapathy S, Mittal BR, Sood A, Sood A, Kapoor R, Gupta R. Peptide receptor radionuclide therapy as first-line systemic treatment in advanced inoperable/metastatic neuroendocrine tumors. Clin Nucl Med. 2020;45:e393–9.
[50] Becx MN, Minczeles NS, Brabander T, de Herder WW, Nonnekens J, Hofland J. A clinical guide to peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE in neuroendocrine tumor patients. Cancers (Basel). 2022;14:5792.
[51] Brabander T, van der Zwan WA, Teunissen JJM, et al. Pitfalls in the response evaluation after peptide receptor radionuclide therapy with [177Lu-DOTA0,Tyr3]octreotate. Endocr Relat Cancer. 2017;24:243–51.
[52] de Wit MC, de Bruin HG, Eijkenboom W, Sillevis Smitt PA, van den Bent MJ. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. Neurology. 2004;63:535–7.
[53] Hicks RJ, Kwekkeboom DJ, Krenning E, et al.; Antibes Consensus Conference participants. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology. 2017;105:295–309.
[54] Halfdanarson TR, Mallak N, Paulson S, et al. Monitoring and surveillance of patients with gastroenteropancreatic neuroendocrine tumors undergoing radioligand therapy. Cancers (Basel). 2023;15:4836.
[55] Allegra C, Blanke C, Buyse M, et al. End points in advanced colon cancer clinical trials: a review and proposal. J Clin Oncol. 2007;25:3572–5.
[56] Shinno Y, Goto Y, Watanabe S, et al. Evaluation of time to failure of strategy as an alternative surrogate endpoint in patients with lung cancer with EGFR mutations. ESMO Open. 2018;3:e000399.