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Quality of life in patients with metastatic gastroenteropancreatic neuroendocrine tumors receiving peptide receptor radionuclide therapy: information from a monitoring program in clinical routine

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Running title

Quality of life in neuroendocrine tumors

ABSTRACT

We evaluated health-related quality of life (HRQoL) in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEPNET) over the course of first peptide receptor radionuclide therapy (PRRT) to first restaging, and compared scores with general population (GP) norms. Methods: We used data from routine HRQoL monitoring with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. Patients received 4–6 cycles of ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC. To be eligible for analysis, patients had to have at least one HRQoL assessment before PRRT and one after treatment completion. Linear mixed models were used to consider HRQoL changes over time. Results: A total of 61 GEPNET patients (small intestine: $N = 37$; pancreatic: $N = 24$) were eligible for analysis. Clear improvements from baseline to first restaging were found for diarrhea in small intestine NET patients showing a clinically relevant decrease of 16 points. We observed a clinically relevant decrease in appetite loss (17 points), but for female small intestine patients only. Other HRQoL changes were also restricted to sociodemographic/clinical subgroups and mainly reflected improvements, except for physical and social functioning showing decreasing scores in older small intestine NET patients. Compared to HRQoL GP norms, patients had impairments in diarrhea, fatigue, appetite loss, physical, social, role functioning, and global HRQoL. Except for diarrhea and appetite loss, patient scores at first restaging did not reach GP levels. Conclusion: Our analyses support previous findings of stable HRQoL under PRRT. Yet, this must not belie patients' significant HRQoL impairments compared to the GP.

Keywords: gastroenteropancreatic neuroendocrine tumors; peptide receptor radionuclide therapy; health-related quality of life; clinical practice; routine monitoring

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEPNET) are considered a relatively rare disease, although incidence rates have almost doubled over the past three decades (*1,2*). They may be asymptomatic for years and are often diagnosed in an advanced stage (*3-5*). Progress in the management of the disease has contributed to increased long-term survival rates (*2,6,7*), and therefore to an increasing percentage of patients in palliative care wherehealth-related quality of life (HRQoL) is of special significance (*3,8*).

While HRQoL is an important outcome in clinical trials in oncology, its assessment in the field of NET research has a young tradition, and knowledge is still limited (*9,10*). Evidence from studies including heterogenous clinical subgroups suggest that NET patients perceive their overall HRQoL as relatively good (*11-13*). However, specific physical and psychosocial complaints are often reported, such as poor physical, emotional, and social functioning, impaired sleep, and significant levels of fatigue (*10-17*). Molecular targeted treatments, such as peptide receptor radionuclide therapy (PRRT), have shown to be effective in terms of both symptomatic control and survival (*8,18-21*). PRRT is generally well tolerated (*18,21-23*) and evidence from studies including patient outcomes suggests favorable outcomes in terms of HRQoL (*20,24-29*).

In recent years, there is growing awareness of the need to incorporate HRQoL assessment not only into clinical trials, but also routine clinical practice, where it positively impacts a range of patient and clinical care outcomes (*30-33*). Such "real-world" data from outside an idealized study setting provide additional valuable information on patients' perceptions of disease and treatment to those obtained from randomized controlled trials (*34*).

To the best of our knowledge, to date, there is no published routine HRQoL data obtained from NET patients. Therefore, we aimed at evaluating HRQoL under such real-world conditions in metastatic GEPNET patients receiving first PRRT by analyzing HRQoL data collected in daily clinical routine. Specific study aims were:

1. To investigate HRQoL of metastatic GEPNET patients over the course of first PRRT. We tested the following hypotheses:
    - Hypothesis 1: For small intestine and pancreatic NET patients we expected changes from baseline to first restaging for fatigue, pain, nausea/vomiting, appetite loss, physical, social, role, and emotional functioning.
    - Hypothesis 2: For small intestine NET patients, we additionally expected changes from baseline to first restaging for diarrhea.

    Changes on other HRQoL aspects were investigated on an explorative basis.

2. To compare patients' HRQoL scores with those of a matched sample from the Austrian general population (GP).

MATERIALS AND METHODS

Patients and data collection

The data set used for analyses was obtained from HRQoL monitoring at the Department of Nuclear Medicine, Medical University of Innsbruck. Patients are admitted at the Department for treatment or follow-up examinations involving radiopharmaceuticals. The routine course at our site is: staging with ^{68}Ga-DOTATOC-PET, 4 cycles of PRRT every 10–12 weeks, restaging after 3 months with ^{68}Ga- DOTATOC-PET and in 6-monthly intervals thereafter. Radionuclides used are ^{90}Y-DOTATOC (^{90}Y), ideally for single, larger lesions, and ^{177}Lu-DOTATATE (^{177}Lu) for smaller lesions. As a result of non-availability, this indications cannot not always be applied.

Patients are invited to participate in HRQoL monitoring at each inpatient visit. Eligibility criteria for HRQoL monitoring are: diagnosis of cancer, age ≥18 years, no brain metastases, no diagnosis of dementia or overt cognitive impairment. Patients are approached by the nursing staff during the admission procedure and asked to complete the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). For more details on the monitoring see Gamper et al. (*35*).

We obtained HRQoL information from the monitoring data set, and sociodemographic and clinical data from medical records. For this type of retrospective investigation, no separate ethical approval and no formal consent have to be obtained according to Austrian law.

Age- and sex-matched population-based controls were taken from a set of previously collected norm data for the QLQ-C30 including 2,000 subjects of the Austrian GP. Details on sampling and data collection are provided elsewhere (*36*).

HRQoL assessment time points

From the large number of HRQoL assessments, we extracted those related to clinically relevant time points:

- T1 (baseline): admission for 1st PRRT cycle (before administration; no octreotide 4 weeks before)
- T2 (during-treatment): admission for 2nd PRRT cycle (2 months after baseline)
- T3 (during-treatment): admission for last PRRT cycle (cycle 4–6; 4–6 months after baseline)
- T4 (follow-up): admission for 1st restaging (3 months after last cycle; no octreotide 4 weeks before)

To be included in analysis, patients had to have completed at least a T1 and a T3 or T4 HRQoL assessment.

HRQoL questionnaire

HRQoL was assessed using the EORTC QLQ-C30 (*37*), one of the most widely used cancer-specific HRQoL questionnaires with good psychometric properties. It consists of 30 items constituting 5 functioning scales (physical, role, emotional, social, cognitive), 9 symptom scales and single items (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global HRQoL scale. Raw scores were linearly transformed to a scale of 0–100 with higher scores reflecting a higher level of functioning and symptomatology, respectively (*38*). Changes in EORTC QLQ-C30 mean scores of 5–10 points were considered as "small", of 10–20 points as "moderate", and of more than 20 points as "large" (*39*).

Statistical analysis

Aim 1: course of HRQoL from T1 to T4. Analyses were performed separately for small intestine and pancreatic NET, as they were considered to be associated with different HRQoL issues. Linear mixed models were used to handle unbalanced data. To account for correlations between repeated assessments, we used a first order autoregressive *[AR(1)]* covariance structure and included "subject" as random factor. The EORTC QLQ-C30 domains were included as dependent variables. Assessment time point (T1–T4), sex, age (dichotomized at median), progression within 1 year after treatment completion (yes/no), and radionuclide for PRRT (^{90}Y/^{177}Lu) were included as independent variables. Interaction effects between assessment time point and other independent variables were tested to investigate whether the course of HRQoL was different between subgroups. We used an alpha-level of ≤0.5 for hypothesis testing and of ≤0.1 for explorative analyses.

Aim 2: HRQoL differences between GEPNET patients and the GP. Two-way analysis of variance was performed with group (patients/GP), sex, and age as factors.

Statistical analyses were performed using IBM SPSS V 22.0.

RESULTS

Patient characteristics

From 2005 to 2014, 133 GEPNET patients were eligible for routine HRQoL monitoring. Of these, 37 small intestine NET (mean age = 62.8 years; 40.5% female) and 24 pancreatic NET (mean age = 61.0 years; 37.5% female)

patients completed at least a T1 and a T3 or T4 HRQoL assessment and were therefore eligible for analysis (min. T1 and T3 or T4 HRQoL assessment). PRRT was given as first-line treatment in 30 small intestine (81.1%) and 17 pancreatic (70.8%) NET patients. ^{90}Y was used in 29.7% of small intestine and 37.5% of pancreatic NET patients. The vast majority of patients completed 4 cycles of PRRT. For details on sociodemographic and clinical characteristics see Table 1.

HRQoL in small intestine NET patients

Comparison of small intestine NET patients' HRQoL scores at T1 with those of GP controls revealed clinically relevant differences to the detriment of patients for diarrhea (+26.6 points, $p < 0.001$), appetite loss (+15.9 points, $p = 0.009$), fatigue (+13.2 points, $p = 0.024$), physical functioning (-10.0 points, $p = 0.036$), social functioning (-13.1 points, $p = 0.014$), role functioning (-14.8 points, $p = 0.033$), and global HRQoL (-11.6 points, $p = 0.019$).

Investigating the course of HRQoL from T1 to T4, the most pronounced change in small intestine NET patients was a clinically relevant improvement in diarrhea (-16.3 points, $p = 0.008$). An improvement over time was also found for appetite loss, but in women only (interaction $p = 0.001$). Female patients had relatively high baseline scores, which, despite a significant and clinically relevant decrease of 17 points, were still clearly higher (+22 points) at T4 than male patients' scores. For the functioning domains, change patterns were less clear. Significant interaction terms between assessment time point and age for physical ($p = 0.044$) and social functioning ($p = 0.035$) indicated age-related effects. Baseline functioning levels of both domains were higher in patients above the median age of 62 years than in those ≤62 years, and the course of functioning from T1 to T4 differed between the age groups with older patients reporting decreasing scores. The mean decrease of social functioning shown in Figure 1 was not statistically significant after accounting for the interaction with age. No changes from T1 and T4 were found in any of the other domains. Overall, older patients >62 years reported significantly more pain than younger patients. Mean score differences between T1 and T4 shown in Figure 2 did not reach statistical significance.

At T4, mean differences regarding fatigue and the functioning domains were smaller, but still statistically significant (fatigue: +3.7 points, $p = 0.017$; physical functioning: -3.1 points, $p = 0.013$; social functioning: -5.7 points, $p = 0.001$; role functioning: -4.2 points, $p = 0.019$) (not accounting for age group differences), while for diarrhea and appetite loss (not accounting for sex differences) there was no longer a statistically significant difference to GP scores (diarrhea: +2.8 points, $p = 0.070$; appetite loss: +3.2 points, $p = 0.052$).

Figure 1 shows symptom and functioning trajectories over treatment including GP scores for domains with significant changes between T1 and T4; for the remaining domains see Figure 2.

HRQoL in pancreatic NET patients

Significant interactions regarding social and emotional functioning indicated significant changes over time for specific treatment and sociodemographic subgroups only. Social functioning improved from T1 to T4 in patients treated with ^{90}Y (+37.1 points). Scores approximated those of patients treated with ^{177}Lu, which did not change significantly over time (interaction $p = 0.008$). Emotional functioning clearly improved in male (+17.1 points), while it slightly decreased in female patients (-5.7 points) (interaction $p = 0.013$). For role functioning, we found no clear pattern for the significant interaction term ($p = 0.005$). No changes from T1 and T4 were found in any of the other domains.

Differences on a range of domains in association with the type of radionuclide were found. Compared to ^{90}Y, ^{177}Lu was associated with less fatigue (-27.7 points, $p = 0.020$), better physical functioning (+22.4 points, $p = 0.050$), cognitive functioning (+23.1 points, $p = 0.003$), and global HRQoL (+17.3 points, $p = 0.029$).

Statistical analyses to compare pancreatic NET patients' and GP HRQoL scores were renounced due to limited number of patients. Figure 3 shows HRQoL trajectories over time for domains with significant changes; for the remaining domains see Figure 4.

DISCUSSION

The present investigation aimed at investigating the course of HRQoL in patients with metastatic GEPNET undergoing first PRRT. We expected HRQoL changes over the course of treatment both as a result of efficient palliation of symptoms (*18,40,41*) as well as accumulation of radioactivity towards the end of PRRT (*42*).

In small intestine NET patients, we found significant impairments at baseline compared to the GP regarding physical, social, role functioning, fatigue, diarrhea, and appetite loss, which has also been reported in NET patients receiving treatment other than PRRT (*14,16,17,43,44*). Most of these differences were still observed at T4, except for diarrhea, a cardinal symptom in these patients, as well as appetite loss, which both reached GP levels. Clinical studies on PRRT for GEPNET showed HRQoL improvements on different symptom and functioning domains over the course of treatment (*20,24-29*). In our analysis of small intestine NET patients, most changes between T1 and T4 were observed in sociodemographic subgroups only. For appetite loss, we found women to report more symptoms than men

throughout treatment and follow-up, with considerable improvements after baseline. Sex differences in the somatic experience of emotional distress (*45-47*) may be considered here. Besides the reported improvements, we found most HRQoL scores to be stable over time, except worsening of physical and social functioning observed in older patients >62 years, which warrants further investigation of (NET-specific) issues not assessed by the EORTC QLQ-C30.

Results on HRQoL in pancreatic NET patients require cautions interpretation due to small sample size. The main result here is that patients treated with ^{90}Y already at baseline reported lower HRQoL on a range of domains (e.g. physical functioning, global HRQoL) than those treated with ^{177}Lu. These effects may be owed to the fact that ^{90}Y usually is administered in patients with larger lesions, which may be associated with higher symptomatology. Unfortunately, we were not able to compare pancreatic NET patients' HRQoL scores with the GP due to lack of statistical power.

Placing our results in the context of clinical GEPNET studies on targeted treatments, such as everolimus and sunitinib, is limited by the lack of HRQoL data in these patients (*48*). However, available studies suggest that HRQoL is maintained over the course of treatment. In the phase 3 RADIANT-4 trial (*49*), where HRQoL was assessed as secondary outcome, patients with advanced gastrointestinal or lung NET treated with everolimus reported stable HRQoL over time with no significant differences compared to a placebo group. Similarly, in a phase 3b study (*50*) HRQoL in patients with pancreatic NET remained stable, while there was a slight decrease in patients with midgut NET. Results from a phase 3 study of sunitinib (*51*) showed stable HRQoL, except for diarrhea and insomnia, which worsened with sunitinib compared to placebo. Largely consistent with these findings, we mainly observed stable or even improved HRQoL scores over the course of PRRT until first restaging, which further supports existing evidence.

A major limitation of the present work is related to the sample size. As data is primarily collected for use in clinical routine, there are various reasons for missing questionnaires (e.g. patient admission timing). We performed a crude comparison of sociodemographic basic characteristics of included and excluded patients showing no statistically significant differences regarding age and sex. We can, however, not exclude a selection bias, especially in terms of overrepresentation of patients with high baseline functional status according to the Karnofsky performance status, which was between 90 and 100 in the majority of patients included in analysis. Also, we cannot make assumptions about the HRQoL "preserving" effect of PRRT due to the lack of a control group.

Another limitation is that we could draw on QLQ-C30 information only, which covers general HRQoL aspects, but may miss NET-specific issues. Currently, two NET-specific HRQoL instruments are available: the QLQ-GI.NET21 (*52*), a module to be applied together with the core questionnaire QLQ-C30, and the Norfolk QOL-NET

(*53*), both including questions on e.g. endocrine and gastrointestinal symptoms, sexual functioning, and depression. In the light of emerging precision medicine concepts, such disease- and/or treatment-specific data may add considerable value to existing knowledge of HRQoL in these patients (*54*,*55*). At our Department, the QLQ-GI.NET21 has been implemented, but has so far been administered to a limited number of patients.

Despite the limitations of the here presented approach of processing HRQoL information, the perspective on patients' HRQoL from outside a clinical study setting is a major strength of the present investigation. Routinely collected HRQoL data is of great importance as it reflects a real-world pattern of treatment and care. Especially in rare diseases such as NET, where clinical studies with sufficient power are more difficult to conduct, such information can contribute to a better understanding of HRQoL issues. With increasing efforts to integrate the patient's voice into the assessment of care quality, the use of HRQoL in performance measurement could also contribute to effectiveness evaluation of treatments such as PRRT (*56*,*57*).

CONCLUSION

The present analysis of routine HRQoL data from patients with metastatic GEPNET undergoing first PRRT indicated improved or at least stable HRQoL on a number of domains from baseline to first restaging. While thereby supporting previous evidence from clinical PRRT studies in these patients, results clearly show patients' significant HRQoL impairments compared to the GP.

DISCLOSURE

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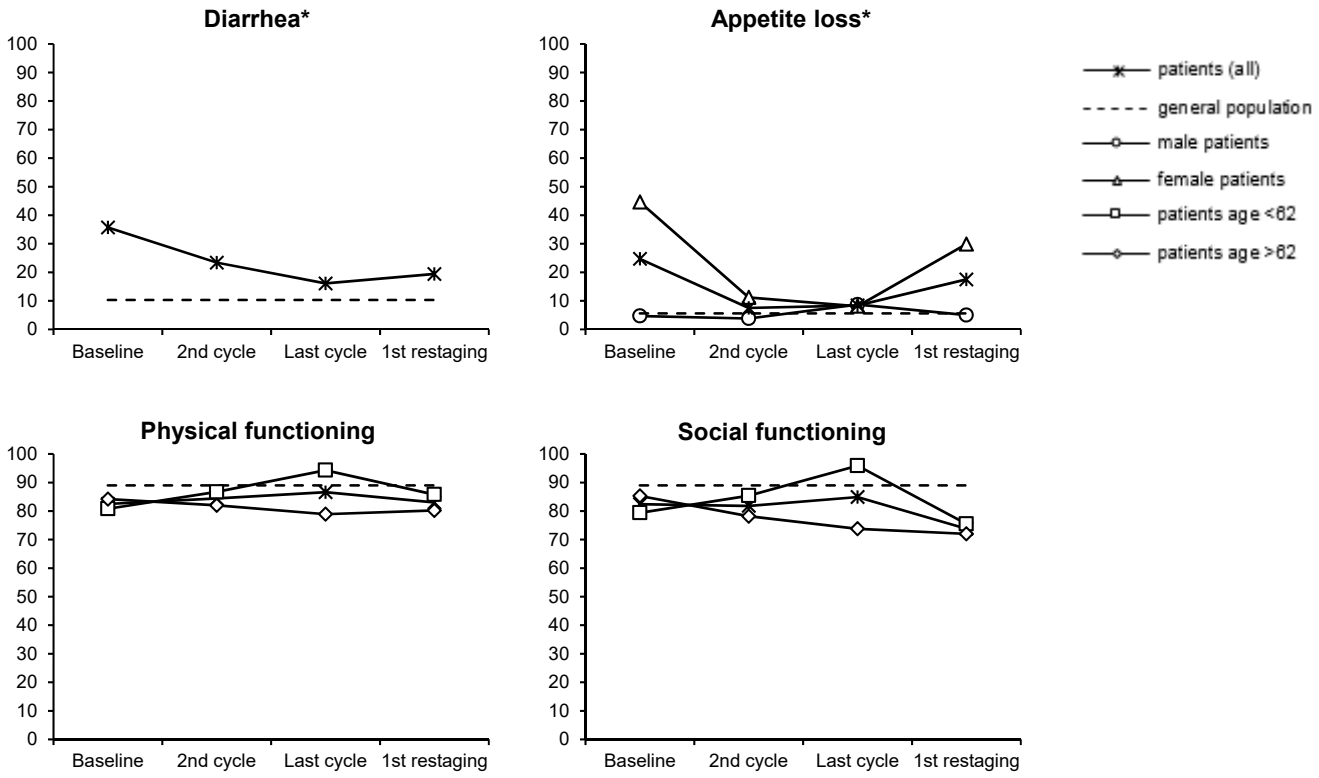
Table 1. Sociodemographic and clinical characteristics for small intestine and pancreatic NET patients.

	Small intestine NET (*N* = 37)	**Pancreatic NET (*N* = 24)**
Age, yrs		
Mean (*SD*)	62.8 (11.9)	61.0 (12.6)
Range	37–88	37–88
Sex, no. (%)		
Male	22 (59.5)	15 (62.5)
Female	15 (40.5)	9 (37.5)
Marital status, no. (%)		
Single	4 (10.8)	3 (12.5)
Partnership/marriage	24 (64.9)	18 (75.0)
Divorced/separated	5 (13.5)	1 (4.2)
Widowed	3 (8.1)	2 (8.3)
Missing	1 (2.7)	-
Employment status, no. (%)		
Employed	4 (10.8)	3 (12.5)
Self-employed	1 (2.7)	20 (83.3)
Retired	28 (75.7)	1 (4.2)
Missing	4 (10.8)	-
Karnofsky score at baseline		
Mean (*SD*)	98.5 (3.6)	91.4 (12.0)
Range	90–100	60–100
PRRT, no. (%)		
^{177}Lu-DOTATATE	26 (70.3)	15 (62.5)
^{90}Y-DOTATOC	11 (29.7)	9 (37.5)
PRRT cycles received, no. (%)		
3 cycles	-	2 (8.3)
4 cycles	29 (85.3)	19 (79.2)
5 cycles	4 (10.8)	3 (12.5)
6 cycles	1 (2.7)	-
Previous treatment, no. (%)		
Surgery	25 (67.6)	8 (33.3)
Chemotherapy	5 (13.5)	6 (25.0)
Radiation therapy	1 (2.7)	1 (4.2)
Biological therapy	3 (8.1)	2 (8.3)
Targeted therapy	3 (8.1)	2 (8.3)
Chemoembolization	1 (2.7)	-
Radiofrequency ablation	2 (5.4)	-
Somatostatin analogues	32 (86.5)	12 (50.0)
HRQoL assessments, no. (%)		
Baseline (T1)	37 (100.0)	24 (100.0)
2nd cycle (T2)	28 (75.7)	19 (79.2)
Last cycle (T3)	27 (73.0)	17 (70.8)
1st restaging (T4)	26 (70.3)	14 (58.3)
Progression within 1 year after first PRRT, no. (%)		
Yes	10 (27.0)	8 (33.3)
No	21 (56.8)	15 (62.5)
Missing	6 (16.2)	1 (4.2)



*no statistically significant difference between mean scores at 1st restaging and GP scores

Figure 1. Course of HRQoL domains with significant changes between baseline and 1st restaging in small intestine NET patients compared to GP.

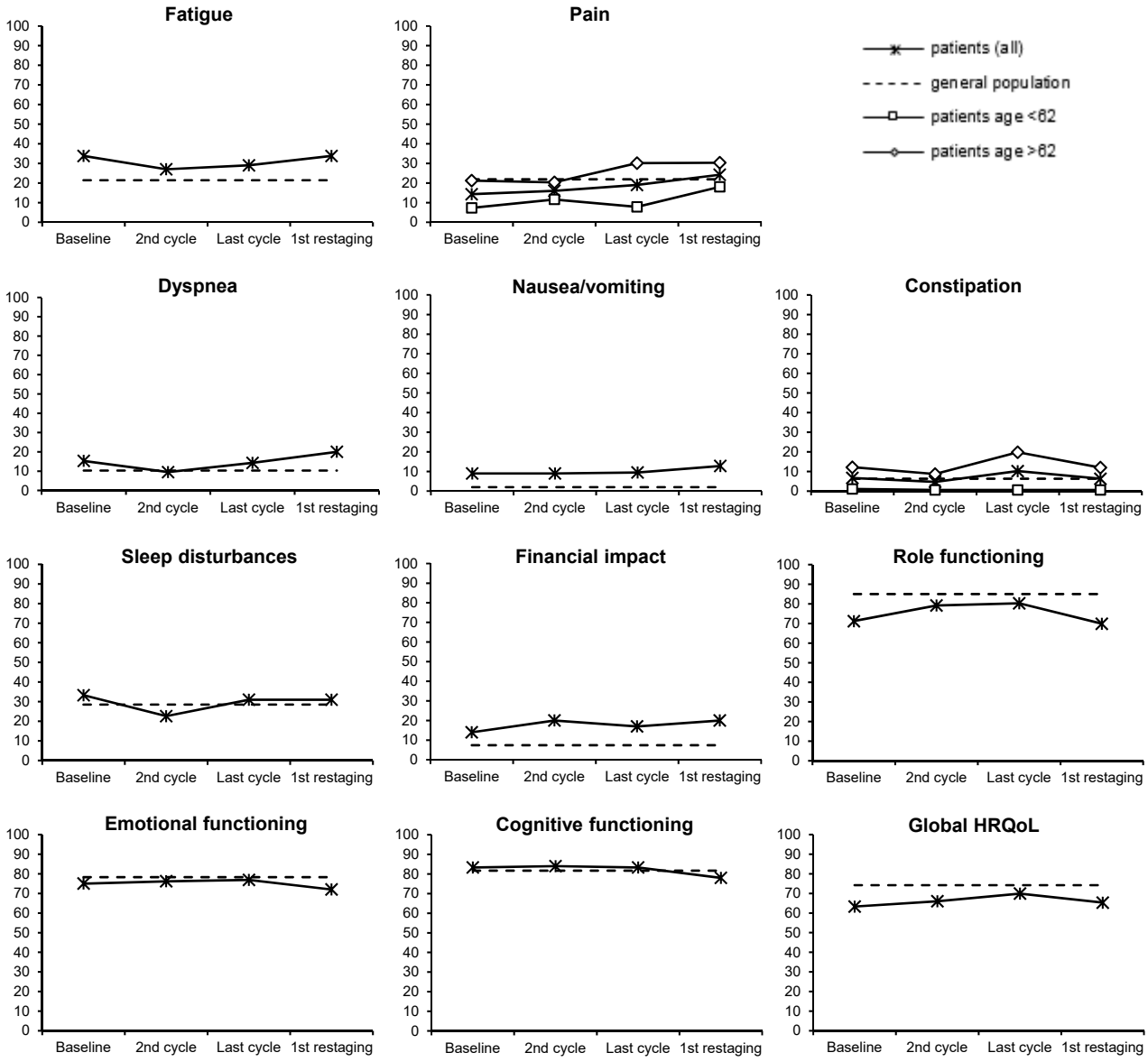


Figure 2. Course of HRQoL domains without significant changes between baseline and 1st restaging in small intestine NET patients compared to GP.

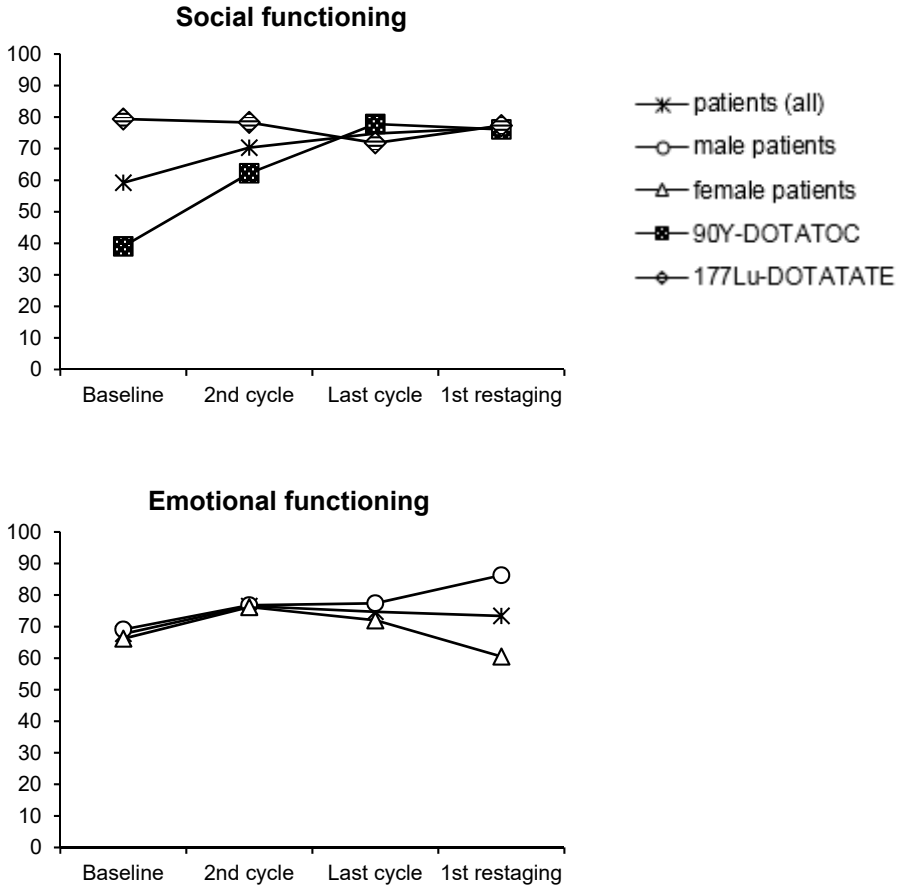


Figure 3. Course of HRQoL domains with significant changes between baseline and 1st restaging in pancreatic NET patients.

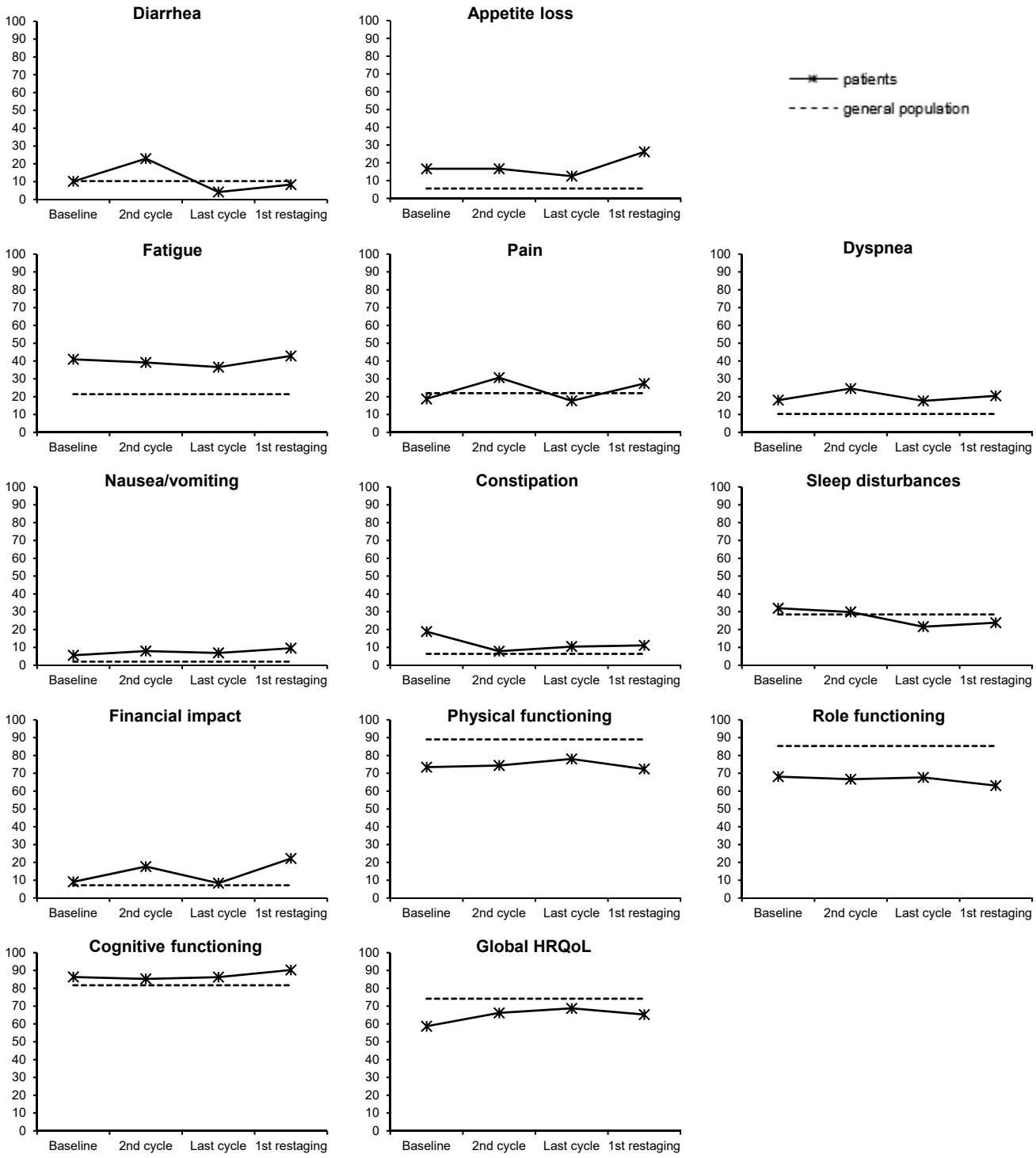


Figure 4. Course of HRQoL domains without significant changes between baseline and 1st restaging in pancreatic NET patients compared to GP.