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ORIGINAL ARTICLE

Quality of life in patients with midgut NET following peptide receptor radionuclide therapy

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Abstract

Objectives There is convincing evidence that peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE compared to octreotide therapy has a positive effect on overall survival and progression-free survival in midgut neuroendocrine tumors (NET). The current study analyzed health-related quality of life (QoL) in patients undergoing PRRT with a special focus on differences in functional performance.

Materials and methods In our study, 70 patients (39 men or 31 female) suffering from midgut NET were included, with a mean age of 64.2 years. Functional performance was assessed by the index of the Eastern Cooperative of Oncology Group (ECOG). Thirty-three patients (47%) showed ECOG 0, 31 patients (44%) ECOG 1, and six patients (9%) ECOG 2. Health-related QoL was assessed by the EORTC QLQ-C30 questionnaire filled in at baseline and 3 months after each PRRT cycle.

Results The median cumulative administered activity was 27.4 GBq. Global health status significantly improved compared to baseline status after 1st ($p = 0.05$), 2nd ($p = 0.004$), and 3rd ($p = 0.04$) treatment cycle. Analyzing specific aspects of QoL, emotional functioning significantly improved after 1st and 2nd treatment cycle (both $p < 0.001$) as well as after 3rd cycle ($p = 0.001$). With regard to cognitive functioning, there was a significant improvement after 1st and 2nd treatment cycle ($p = 0.003$ and $p = 0.05$ respectively). With regard to alleviation of somatic symptoms, a significant reduction in pain and diarrhea was observed after the 2nd cycle ($p = 0.038$) and 3rd cycle ($p = 0.036$). Furthermore, changes in QoL in relation to functional performance status as assessed by ECOG were analyzed. There were no significant differences with regard to QoL alterations between patients with high (ECOG 0 or 1) and moderate performance status.

Conclusion Our study confirmed an equally positive effect of PRRT on quality of life in midgut NET patients with high or moderate functional status in terms of increasing global health, functional status, and alleviating symptoms.

Keywords PRRT · MIDGUT NET · ^{177}LU-DOTATATE · QOL

Milka Marinova and Martin Mücke share first authorship, Rupert Conrad and Hojjat Ahmadzadehfar share senior authorship

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Introduction

Neuroendocrine tumors (NETs) represent a wide spectrum of diseases. NETs of the midgut are rare and are often represented by very small primary tumors which can be hardly visualized at imaging. At the time of diagnosis, patients often have extensive liver and nodal metastases and may experience symptoms secondary to the release of active substances by the primary tumor, such as serotonine and its metabolites with local and systemic effects. Systemically, the release of active substances into the circulation can cause carcinoid syndrome including flushing, diarrhea, and abdominal pain [1, 2]. This may severely affect quality of life in all relevant emotional, social, and physical aspects of the individuals' life [3]. The influence of disease on quality of life is captured in the construct of health-related quality of life. Against this backdrop, many randomized controlled trials [4–10] analyzed the impact of different treatments for NETs on health-related quality of life (HRQoL).

Based on the use of a receptor target, peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATAE represents one of the most effective and well-tolerated treatment options for well-differentiated unresectable or metastatic neuroendocrine tumors. NETs have shown a high response rate to the low toxic PRRT, while a further positive impact on survival has been observed [11–26].

As mentioned above, health-related quality of life (QoL) has become a major issue when assessing the outcome of therapeutic interventions. Mainly in patients with malignancies, subjectively perceived global health status, functional performance, and disease symptoms define the health-related QoL according to the European Organisation for Research and Treatment of Cancer, which is a crucial player in preserving patients well-being and their ability to stay in the community for a long time [27, 28]. The option to take part in daily life and perform a wide range of daily activities acts towards ensuring a successful medical treatment of cancer patients.

Nowadays, most NET patients could have a long life specifically due to available therapies, so that keeping a good health-related QoL is of particular importance for these patients. As midgut NET is associated with a wide spectrum of burdensome symptoms, PRRT could be an important coplayer in coping with this malignancy alongside supportive palliative care [29]. The following study sheds light on changes in health-related QoL of affected patients following PRRT.

We hypothesized that PRRT significantly improves global health status as measured by the EORTC QLQ-C30 of midgut-NET patients. Furthermore, we hypothesized that there would be no significant difference in the improvement of global health status between patients with no (ECOG 0) and moderate (ECOG 1–2) functional impairment. In further explorative analyses, changes in EORTC QLQ-C30 subscales on functional performance and symptomatology were analysed.

Methods

Patient selection

In this study, the data of 89 patients with metastatic midgut NET who received PRRT between 2007 and 2015 using ^{177}Lu-DOTATATE in the department of Nuclear Medicine, University Hospital Bonn, were retrospectively analyzed. Seventy patients (31 female), mean age 64 years, range 34–83 years, fulfilled the inclusion criteria (Supp. Fig. 1). Of the 70 patients, at baseline 47.1% of patients presented with ECOG 0 and 52.9% with ECOG 1 or 2. Further demographic and clinical characteristics of PRRT-treated patients with midgut NET are summarized in Table 1. The inclusion criteria for this study were: (1) histopathologically confirmed unresectable metastatic midgut NET, (2) completed planned therapy cycles, (3) ECOG 0–2,; (4) at least 3 months follow-up after the last cycle, (5) completed EORTC QLQ-C30 form prior to the first cycle and at least one after the last cycle. All participants signed informed consent for the PRRT treatment. Retrospective analysis was performed according to the ethical guidelines of the ethics commission of the University of Bonn, and the requirement for separate informed consent for this analysis was waived.

Peptide radionuclide receptor therapy (PRRT)

In order to avoid interference with Lu-octreotate, short-acting somatostatin analogues were discontinued for 1 day and long-acting release formulations 4–6 weeks before PRRT. Labelling of the peptide with lutetium-177 (IDB Holland, Baarle-Nassau, The Netherlands) was performed locally. The patients were premedicated intravenously with ondansetron (8 mg) and received an infusion of amino acids (2.5% lysine and 2.5% arginine in 1 l 0.9% NaCl) for over 4–6 h, starting 30 min before therapy. The radiopharmaceutical was administered via an indwelling catheter over 10–20 min. The mean and median administered activity were 7.1 and 7.4 GBq per cycle respectively.

Evaluation of quality of life (QoL)

In our patient cohort, changes in QoL and symptom status following PRRT were assessed using the EORTC QLQ-C30 questionnaire (European Organisation for Research and Treatment of Cancer — Quality of life questionnaire, Version 3.0) in its validated German version [30, 31]. The paper–pencil form of the questionnaire was filled in prior to each PRRT cycle and at least once 3 months after the last

Table 1 Demographic and clinical characteristics of PRRT-treated patients with MIDGUT neuroendocrine tumor according to ECOG status

	All patients	ECOG 0	ECOG 1 and 2	*P* value
Age	64 years (34–83)			
Sex	M: 39 (55.7%)	22	17	0.08
	F: 31 (44.3%)	11	20	
Grading	G1: 35 (50%)	21	14	0.06
	G2: 25 (35.7%)	10	15	
	Unknown: 10 (14.3%)	2	8	
Prior therapies	63 (90%)	32	31	0.07
Operation	50 (71.4%)	26	24	0.19
Biotherapy	51 (72.9%)	22	29	0.27
Chemotherapy	8 (11.4%)	3	5	0.56
Locoregional	5 (7.1%)	1	4	0.20
Documented morphological or clinical progression prior to 1st cycle PRRT	55 (78.6%)	26	29	0.96
Tumour functionality				
Active	58 (83%)	22	36	0.007
Inactive	12 (17%)	11	1	

M = male, F = female

cycle. EORTC QLQ-C30 is a validated 30-item questionnaire of self-reported health-related QoL of cancer patients containing both single- and multi-item measures. These include five functional scales (physical, role, cognitive, emotional, social functioning), three symptom scales (fatigue, pain, nausea/vomiting), a global health status, and six single items (constipation, diarrhea, insomnia, dyspnea, appetite loss, financial difficulties) [31]. Scores for each scale and single-item measure are transformed linearly to a score ranging from 0 to 100 and then tabulated according to guidelines. A high score for functional scales and global health status is desirable, representing better functioning ability, whereas a high score for symptom scales and single items refers to substantial symptomatology. Clinical assessment was performed at baseline and every 3 months following each PRRT cycle up to at least 1 year.

Statistical analysis

Data were analyzed using Stata Version 13.1 (Stata Corp, College Station, TX, USA) and SPSS (Version 22 for Windows, SPSS Inc., Chicago, IL, USA). Mean, median, standard deviation (SD), range, and exact 95% confidence intervals (CI) were estimated. The multivariate dimensions of QoL were assessed using the basic EORTC QLQ-C30 questionnaire. The statistical evaluation of QoL scales was performed using the mixed longitudinal (panel) model allowing for missing data [32, 33]. Due to the low response rate of less than 25% (21.4%) after the fourth cycle, these data were excluded from further analysis. A model with interaction was used for pain, insomnia, and diarrhea. No interaction was found for all other EORTC scales. Results were presented as contrasts (differences) and were verified for susceptibility of model dependency using a non-parametric Skilling–Mack test for unbalanced panel data. To evaluate the effect of ECOG performance status at baseline, semiparametric analysis and generalized linear models were additionally used. A value of < 0.05 was considered statistically significant (Table 2).

Results

Patient characteristics and treatment data

A total of 70 patients (31 female) with midgut NET, mean age 64 years, range 34–83, (Table 1) were treated with PRRT using ^{177}Lu-DOTATATE, while first-line PRRT was performed in seven patients (10%). At presentation, 33 patients had a good ECOG performance status (ECOG 0); 37 patients presented with slightly impaired or more restricted *ECOG* status (ECOG 1 or 2). A total of 52 patients (74%) presented with functioning NET, 35 patients with midgut NET of grade 1, 25 patients of grade 2, grade non-available in ten patients. The median of tumor markers CgA (chromogranin A) and NSE (neuron specific enolase) were 589 ng/ml and 14 ng/ml respectively. Sixty-three patients (90%) underwent one or more than one prior therapies (e.g., surgery, biotherapy, chemotherapy, or locoregional treatment). Prior to the PRRT, a clinical or morphological progress was observed in 55 patients (78.6%).

The median cumulative administered activity was 27.4 GBq (8.36–37.2 GBq). PRRT was performed at least

Table 2 EORTC scores and scales

EORTC[a] scale		Mean (*p*-value)[b] [95% CI][c]			
		Baseline	3 months	6 months	9 months
Global health status		62.6 [58.6; 67.6]	66.7* [61.9; 71.4]	69.6** [64.4; 74.6]	69.4** [62.7; 75.1]
Functional scales	Physical functioning	76.5 [71.7; 81.3]	76.9 [72.1; 81.8]	76.7 [71.7; 81.8]	75.2 [69.8; 80.6]
	Role functioning	66.7 [59.5; 73.8]	69.6 [62.4; 76.9]	67.7 [59.8; 75.5]	67.4 [58.6; 76.1]
	Emotional functioning	64.2 [58.9; 69.4]	73.0*** [67.6; 78.3]	74.9*** [69.1;80.6]	74.2** [67.8; 80.6]
	Cognitive functioning	77.1 [71.9; 82.4]	83.5* [78.2; 88.8]	81.6* [75.9;87..3]	76.8 [70.6; 82.9]
	Social functioning	70.9 [64.5; 77.4]	75.8 [69.1; 82.4]	76.2 [69.1; 83.4]	74.9 [66.8; 82.9]
Symptom scales and single items	Fatigue[1]	36.7 [30.6; 42.7]	32.7 [26.6; 38.9]	32.7 [26.2; 39.2]	34.4 [27.3; 41.5]
	Nausea and vomiting[1]	4.1 [1.8; 6.4]	3.9 [1.5; 6.2]	3.0 [0.3; 5.6]	4.1 [1.3; 7.2]
	Pain[1]	28.6 [21.9; 35.2]	26.3 [19.5; 33.0]	23.0 * [15.7; 30.4]	24.8 [16.6; 33.1]
	Dyspnoea[2]	26.2 [19.6; 32.8]	28.8 [22.0; 35.6]	28.4 [21.1; 35.7]	29.8 [21.7; 38.0]
	Insomnia[2]	30.5 [22.8; 38.1]	30.9 [23.1; 38.7]	27.8 [19.6; 36.1]	36.7* [27.5; 45.8]
	Appetite loss[2]	11.9 [6.8; 17.1]	8.9 [3.6; 14.2]	11.2 [5.2; 17.1]	13.4 [6.5; 20.3]
	Constipation[2]	8.1 [3.9; 12.3]	6.5 [2.2; 10.8]	3.3 [0.4; 8.0]	5.1 [0.1; 10.4]
	Diarrhea[2]	44.8 [37.1; 52.4]	43.3 [35.5; 51.1]	37.4* [29.0; 45.8]	34.9* [25.4; 44.3]
	Financial difficulties[2]	21.0 [14.7; 27.2]	16.4 [10.1; 22.8]	14.6 [7.8; 21.4]	21.8 [14.3; 29.4]

Baseline values (prior to 1st PRRT cycle) and score/scale values 3 months after 1st, 2nd, and 3rd PRRT cycle as means, and 95% confidence interval of the EORTC-QLQ-C30 scores of patients with MIDGUT neuroendocrine tumor treated by PRRT

[a] EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [0–100]

[b] significant *p* value as compared to baseline: *: < 0.05, **: < 0.01, ***: < 0.001

[c] CI, 95% confidence interval

[1] symptom scales

[2] single items

twice in all patients ($n = 70$), and up to four cycles in 68 patients (four cycles in 50 patients and three cycles in 18 patients).

Quality of life

At baseline, which means prior to 1st cycle PRRT, all patients completed EORTC QLQ-C30 questionnaire. At follow-up, 3 months after 1st, 2nd, 3rd, and 4th PRRT cycle, the questionnaire was available from 65, 50, 35, and 15 patients respectively. Considerable differences over time were shown on functional and symptom status (Figs. 1 and 2). Compared to baseline, QoL was significantly improved, revealing increased global health status (3 months after 1st, 2nd, and 3rd treatment cycle $p = 0.049$, $p = 0.004$, and $p = 0.041$, respectively) (Fig. 1). In addition, functional scale responses such as emotional and cognitive functioning showed also considerable improvement over time following PRRT (emotional functioning: 3 months after 1st and 2nd cycle $p < 0.001$, after 3rd cycle $p = 0.001$; cognitive functioning 3 months after 1st cycle $p = 0.003$, after 2nd cycle $p = 0.05$) (Fig. 1). Other functional scales such as physical, role, and social functioning were maintained over time. Furthermore, some symptom scales and single items representing symptomatology were significantly alleviated after PRRT compared with baseline: pain (after 2nd cycle $p = 0.038$), insomnia (after 3rd cycle $p = 0.033$), diarhoea (after 2nd cycle $p = 0.05$, after 3rd cycle $p = 0.02$) (Fig. 2). Other values of symptomatology, even if not significantly changed, did not increase after PRRT and remained stable over time. The presented effects on QoL functional and symptom status were also found within ECOG-divided groups (ECOG0 and ECOG 1 and 2) (Figs. 1 and 2). The therapy was equally beneficial in patients with very high as well as moderate functional status.

Discussion

In our study we aimed at analyzing quality of life in midgut NET patients treated by PRRT. Even though there is an increasing interest in health-related QoL in NET patients, there is still a lack of knowledge on this issue due to the scarceness of methodologically sound studies [34]. The signs and symptoms of midgut NET usually occur as a result of either mechanical complications such as bleeding or obstruction, or due to the release of vasoactive peptides into the bloodstream [35, 36]. These vasoactive peptides (e.g., serotonin, histamine, tachykinin) can produce a wide range of dermatological,

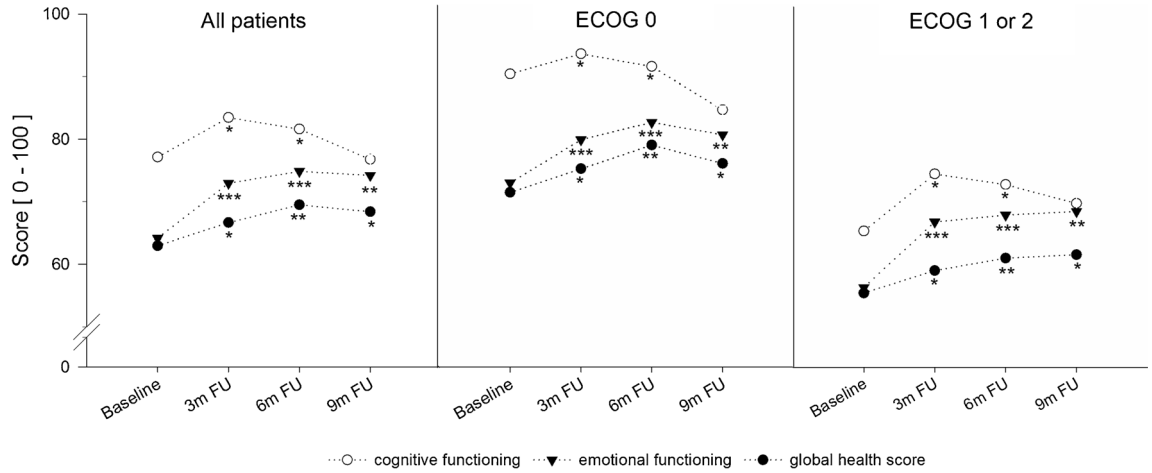

Fig. 1 Significant changes in global health status and functional scales (cognitive and emotional functioning) over time following PRRT in patients with MIDGUT-NET, evaluated by EORTC QLQ-C30

gastrointestinal and cardiovascular symptoms subsumed under the term carcinoid syndrome. In particular, patients may suffer from abdominal cramping, diarrhea, flushing, telangiectasias, bronchospasms, valvular lesions, and rarely pellagra [2]. Carcinoid syndrome has been reported to occur in approximately one third of patients with midgut NETs [35]. In particular, the variety of symptoms associated with carcinoid syndrome and the sudden and unpredictable onset of symptoms may deeply affect patients' health related QoL. The most important target of treatment is sufficient control of symptom burden, thereby stabilizing or increasing health-related QoL [27]. In this context, previous studies have proved that PRRT is highly effective in reducing specific symptoms of the carcinoid syndrome such as diarrhea and flushing, as well as cardiac function disorders due to right ventricular dysfunction [37]. The seminal NETTER1 trial investigated 231 patients, and showed that time to QoL deterioration was significantly longer in the ^{177}Lu-DOTATATE arm than in the high-dose octreotid control arm for the domains global health status, physical functioning, role functioning, fatigue, pain, diarrhea, disease-related worries, and body image as measured by the EORTC-QLQ-C30 [38]. One patient from this trial [39] even showed a stable disease after four cycles of PRRT, with excellent quality of life (full working hours) persisting for 3 years of follow-up. This is in accordance with previous reports of overall stable health-related QoL under PRRT [31]. Against this backdrop, our study took a closer look at the course of QoL over up to three PRRT treatment cycles, taking into account the performance status as measured by ECOG. Our findings showed an improvement in global health status, emotional functioning, and cognitive functioning compared to baseline 3 months after both 1st and 2nd treatment cycles. Thus, our hypothesis was confirmed. Inferential statistics unveiled no significant deterioration of functioning scales in the course of PRRT treatment. Positive experiences at the beginning of treatment are of particular importance, as they alleviate potential fears of the patient with regard to treatment and may improve treatment adherence [40, 41]. Further analysis also revealed a significant improvement in global health

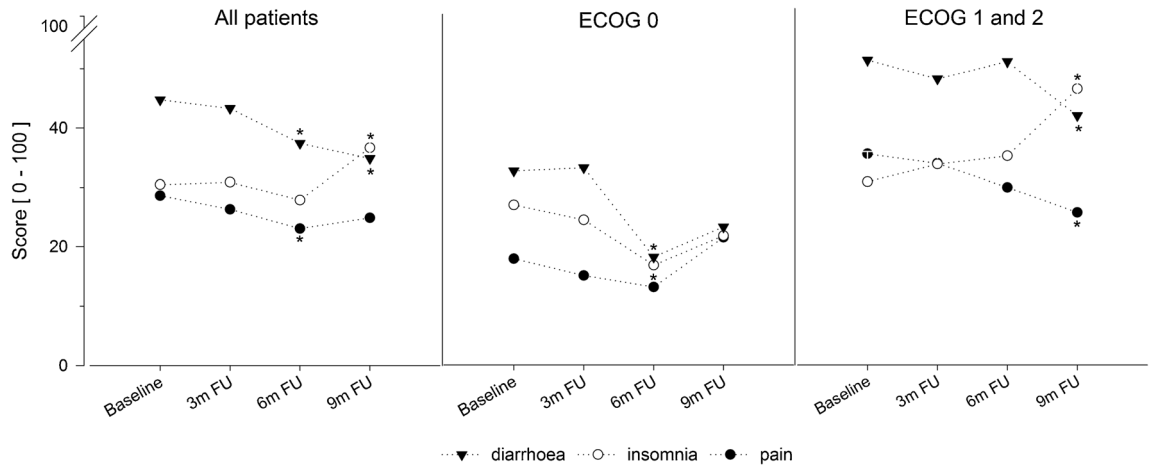

Fig. 2 Significant changes in tumor-related symptoms (diarrhoea, insomnia, pain) over time following PRRT in patients with MIDGUT-NET, evaluated by EORTC QLQ-C30

status and emotional functioning in the patients undergoing a 3rd treatment cycle. The scale 'emotional functioning' asks patients whether they worry or feel tense, irritable, or depressed, assessing core symptoms of psychological well-being. With regard to improvement of somatic symptoms, our findings displayed an alleviation of pain after the 2nd treatment cycle, and of diarrhea after the 3rd treatment cycle. The fact that we could confirm a significant mitigation of both symptoms in the course of treatment, even though disease progression may have counteracted a beneficial effect, can be seen as particularly remarkable. During treatment, patients reported no increase in limitations with regard to work and daily or leisure time activities. This is of particular clinical relevance because cancer treatment often grossly interferes with a wide spectrum of patients' activities, negatively affecting patients' feeling of self-efficacy [42]. These findings underline the positive impact of PRRT on QoL in our clinical sample with midgut NET. Even though the treatment by PRRT is not completely free of side-effects [37], our findings confirm that acute side-effects such as nausea, headache, and exacerbation of neuroendocrine syndrome are usually mild and transient, so that treatment periodicity allows the patient to recover from side-effects, and PRRT does not negatively affect health-related QoL. With regard to performance status at baseline, 47% of our sample were fully active without restrictions imposed by the disease (ECOG 0), whereas 44% were restricted in physically strenuous activities, but able to carry out light work (ECOG 1), and 9% were not able to carry out any work activities (ECOG 2). When comparing the outcome in the fully active group (ECOG 0) to the restricted groups (ECOG 1 and 2), our findings indicate that there were no significant differences regarding the change of QoL as measured by global health status 3 months after the 1st, 2nd, and 3rd PRRT cycle. Analysing the above mentioned ECOG groups 0 and 1/2 separately for alterations in specific symptoms such as pain, insomnia, and diarrhea over the treatment cycles compared to baseline, we found a significantly greater symptom reduction for insomnia and diarrhea 3 months after the 2nd treatment cycle in the ECOG 0 group. Furthermore the analyses showed a significantly greater symptom reduction for insomnia, diarrhea and pain 3 months after the 3rd treatment cycle in the ECOG 1/2 groups. Nevertheless, the comparison of both ECOG groups on respective symptoms over the treatment cycles indicated no significant differences. Against this backdrop, one might argue that patients with a high as well as moderate functional performance status show a comparable change in their health-related QoL as assessed by EORTC questionnaire. However, our study findings do not allow for conclusions concerning PRRT treatment in severely impaired patients (ECOG 3 and 4). With regard to quality of life, our findings are in accordance with the NETTER-1 trial, underlining the positive impact of PRRT on health-related quality of life. This beneficial effect could also be seen in further recent studies investigating PRRT in midgut neuroendocrine tumors. Thus, Martini et al. [43] investigated a sample of 61 patients with gastroenteropancreatic NETs, including 37 patients suffering from small intestine NETs undergoing 4–6 treatment cycles, and found clear improvements from baseline to the first restaging in small-intestine NET patients for diarrhea as well as a clinically relevant decrease in appetite loss in female small-intestine NET patients. Overall analyses showed overall stable HRQoL under PRRT except for specific aspects of health-related quality of life in older small-intestine NET patients, which showed decreasing scores for physical and social functioning. Compared to our study investigating midgut NETs, Martini et al. [43] analysed a smaller sample of patients with small-intestine NETs so that differences in sample size as well as exact tumor sites limit comparability. Furthermore, this study as well as NETTER-1 did not analyse the health-related quality of life in relation to different levels of functional performance. To the best of our knowledge, further recent studies focusing on health-related quality of life in PRRT have focused on pancreatic NETs. Thus, a previous study from our research group [44] confirmed the largely beneficial effect of up to four PRRT cycles on all aspects on quality of life, with significantly improved global health status, social functioning, fatigue, and appetite loss at the end of the study. Similar findings in a sample of 34 pancreatic NET patients were reported by Zandee et al. [45]. Follow-up 3 months after the last treatment cycle was available for 22 patients and showed a significant increase for global health, as well as for physical, role, emotional, and social functioning and a decrease in fatigue.

The specific advantage of PRRT is the possibility to offer a more personalized cancer treatment thereby [42, 46], facilitating maximum damage to tumor cells as well as maximum protection of healthy tissue. Current trials aim at optimizing this personalized treatment by adjusting the injected activity to deliver a prescribed absorbed dose to the kidney to safely increase tumor irradiation [47]. Our findings underline the efficacy of PRRT with fewer and milder side-effects compared to other conservative interventions such as chemotherapy, a significant alleviation of symptom burden, and a positive impact on health-related QoL.

Our study shows the following limitations. The moderate sample size does not allow for the detection of small effects of PRRT treatment on quality of life. The majority of patients showed a high to moderate functional status as measured by ECOG; therefore, our findings cannot easily be transferred to patients with greater functional impairment.

Conclusion

PRRT is a well-tolerated therapy option, proving to be an effective treatment in midgut neuroendocrine tumors. Even though there was no control group in this study, PRRT seems to improve health-related QoL and alleviate symptom burden in patients with high or moderate functional status. Our study

proved the therapy to be equally effective in patients with different functional status.

Compliance with ethical standards

Conflict of interest The authors declare that they have no financial or non-financial competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent All participants signed informed consent for the PRRT treatment. Retrospective analysis was performed according to institutional ethical guidelines, and the requirement for separate informed consent for this analysis was waived.

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