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Improved health-related quality of life during peptide receptor radionuclide therapy in patients with neuroendocrine tumours

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Abstract

Neuroendocrine tumours (NETs) can arise in different locations in the body, and may give rise to hormonal symptoms, which amongst other factors may affect patients' health-related quality of life (HRQoL). Up to four cycles of peptide receptor radionuclide therapy (PRRT) have been shown effective for symptom alleviation and prolonging progression-free survival. The aim of this study was to assess the patient's perspective regarding changes in their HRQoL during PRRT. HRQoL was assessed using the questionnaires for cancer in general, EORTC QLQ-C30, and the gastrointestinal NET-specifically EORTC QLQ-GINET21. Patients with NET ($n = 204$) rated their HRQoL before PRRT cycles one and four. The medical records of patients were reviewed and their HRQoL was compared to a matched reference population ($n = 4910$). HRQoL was found to improve during PRRT in aspects of global quality of life; role, social, and emotional functioning, and multiple symptom relief. Potential risk groups for worse HRQoL during PRRT were patients with overweight (BMI >25) who completed four cycles of PRRT and older patients (>65 years old). In conclusion, we found that PRRT improves HRQoL in patients with NETs. The results of this study may be used to improve person-centred care.

KEYWORDS
HRQoL, NET, PRRT, quality of life

1 | INTRODUCTION

Neuroendocrine tumours (NETs) are rare with an incidence of almost 7 per 100,000 persons per year, equally distributed between females and males.[1,2] Patients may be asymptomatic, or experience uncharacteristic symptoms for years, and are often diagnosed after the disease has metastasized.[3] Contrary to nonfunctioning NETs, functioning NETs are associated with a clinical syndrome related to hormonal excess.[3,4]

Peptide receptor radionuclide therapy (PRRT) with lutetium-177 labelled octreotate (^{177}Lu-DOTATATE) has become an efficient and well-tolerated treatment for symptom control, and also prolongs progression-free survival.[5] The outcome of PRRT is influenced by the NET type, grade and tumour load. The treatment is usually given in four sequential cycles administered every 8–10 weeks.[6]

The patient's satisfaction and health-related quality of life (HRQoL) experience are important variables in the assessment of the quality of care. Also, to be able to discuss how HRQoL may be affected can increase patient participation in treatment choices, and increase person-centred care.[7] These issues may influence the patient's compliance to the treatment and, thus, may have an impact

on treatment outcome.[8] NET symptoms often impair daily life, affecting the patient's emotional health and relationships with relatives, as well as reducing their work ability.[9] Patients with NETs display lower HRQoL than the general population,[10] and the systemic treatments have been shown to worsen HRQoL.[7] Few studies have investigated HRQoL during PRRT, mainly conducted in small cohorts of patients.[11-13] There is therefore a need to further examine patient-experienced HRQoL in conjunction with PRRT. Moreover, differences in HRQoL related to age, gender, and functioning versus nonfunctioning tumour status have not been explored. Knowledge of the patient's HRQoL may facilitate and improve person-centred care. The aim of this study was to investigate the patient's perspective regarding changes in their HRQoL during PRRT.

2 | METHODS

2.1 | Peptide radionuclide receptor therapy (PRRT)

The inclusion criteria for PRRT were tumour somatostatin receptor expression higher than that in the normal liver found on somatostatin receptor scintigraphy (Krenning score 3 and 4), or on ^{68}Ga-DOTATOC positron emission tomography (PET), and sufficient bone marrow, liver and kidney function. DOTATATE was labelled in house with ^{177}Lu (IDB Holland BV, Noord Brabant, Netherlands). The patients were premedicated intravenously 1 h before PRRT with 8 mg of betamethasone and 8 mg of ondansetron, or 250 ug palonosetron, and for kidney protection they received an infusion of amino acids (Vamin, 14 g N/L, electrolyte-free; Fresenius Kabi) over 8 h, starting 30 min before the start of PRRT. ^{177}Lu-DOTATATE was administered as an infusion for 30 min. The mean administered activity was 7.4 GBq per cycle and the intended interval between cycles was 8–10 weeks. Up to nine cycles were given, yet the majority of patients received four cycles of PRRT.

2.2 | Patients and data collection

The study was approved by the Regional Ethics Committee in Uppsala, Sweden (Dnr.2010/177) and written informed consent was obtained from all participants.

Between 2009 and 2018, a total of 756 patients received PRRT with ^{177}Lu-DOTATATE at Uppsala University Hospital. There was 324 (43%) women and 432 (57%) men, and the patients received up to nine cycles. Two questionnaires, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and the EORTC gastrointestinal neuroendocrine tumour cancer-specific module (QLQ-GINET21) were filled in on paper by the patients the day before/at the same day as PRRT. A total of 1665 QLQ-C30 and QLQ-GINET21 questionnaires were obtained. Nonresponse analysis was not performed. Most patients received four cycles of PRRT and therefore those who had filled in the questionnaires the day before/at the same day as cycles 1 and 4 ($n = 204$, 27%) were selected for further analysis. Among them, 124 (61%) with small-intestinal NETs (SINETs), 45 (22%) with pancreatic NETs (PNETs) and 35 (17%) with various other NETs, mainly rectal and lung NETs. The patients' medical records were reviewed regarding functional status (functioning vs. nonfunctioning tumours), gender, age at diagnosis, and at first PRRT, marital and employment status, PRRT cycles received, previous treatments and body mass index (BMI) (Table 1).

2.3 | Health-related quality of life questionnaires

The QLQ-C30 and the QLQ-GINET21 questionnaires were used. The QLQ-C30 consists of 30 items measuring HRQoL aspects in patients with cancer in general and is a sensitive instrument for measuring changes in patient performance status.[14] The disease-specific module, QLQ-GINET21, consisting of 21 items, is a more sensitive assay than the QLQ-C30 regarding NET therapies, including variables to assess treatment toxicity, NET symptoms, and tumour progression.[15,16]

Social functioning and pain are items in both questionnaires, but the questions are expressed differently. In QLQ-C30, the questions regarding social functioning address disturbances in family life and social activities, while QLQ-GINET21 addresses disturbances in daily life, effects on the next of kin, and the ability to travel.

2.4 | Reference population

Patients with NET experiences of HRQoL were compared to those of a reference population. From a large random sample ($n = 4910$) of the Swedish adult population,[17] a reference population of 204 persons was extracted, which was matched to our patient cohort regarding chronical diseases (diabetes, cardiac, respiratory, renal or other specified conditions), age and gender. The reference population completed only the QLQ-C30 questionnaire.

2.5 | Data analysis

Responses to the QLQ-C30 and QLQ-GINET21 questionnaires were linearly transformed to a 0–100 scale with higher scores reflecting better global health status/quality of life, higher levels of functioning or more symptoms, according to the scoring procedure in the EORTC manual.[18] Missing items were handled as recommended in the EORTC scoring manual.[18] HRQoL measures are presented as mean scores and standard deviation (SD). A difference of ≥5 mean scores between the first and fourth treatment cycles was considered clinically relevant, as previously defined.[19] Statistical significance was only calculated for clinically relevant changes (mean score differences ≥5), using the Wilcoxon signed-rank test. A paired t-test was used to compare mean scores before the first and fourth cycles, using the Statistical Package for the Social Sciences (SPSS) version 24.0 (Chicago, IL, USA).

TABLE 1 Characteristics of 204 patients with NETs receiving PRRT.

Characteristics	Patients	SINET	PNET	Others
Patient numbers	204	124	45	35
Functioning tumour	135	105	11	19
Nonfunctioning tumour	69	19	34	16
Sex				
Men	134	83	32	19
Women	70	41	13	16
Age at diagnosis				
<50	47	23	13	10
50–64	96	65	20	12
65–82	61	36	12	13
Age at first therapy				
<50	31	13	9	9
50–64	76	46	20	10
65–85	97	65	16	16
Marital status				
Single	41	25	6	10
Partnership/marriage	159	96	39	24
Widowed	2	1	-	1
Missing	2	2	-	-
Employment status				
Employed	55	34	14	7
Sick leave	33	16	8	9
Retired	85	56	15	14
Missing	31	18	8	5
PRRT cycles received				
4 cycles	79	49	17	13
5 cycles	55	37	9	9
6 cycles	45	27	9	9
7 cycles	17	8	8	1
8 cycles	3	-	-	3
9 cycles	2	2	-	-
10 cycles	1	-	1	-
Previous treatment				
Surgery	125	87	20	18
Chemotherapy	61	9	40	12
Somatostatin analogues	143	114	18	11
Interferon	49	45	3	1
Biotherapy	16	4	9	3
Treatment of metastasis	54	36	11	7
BMI				
≤18.5	6	4	0	2
19–25	102	67	26	9
>25	94	51	19	24
Missing	2	2	-	-

Abbreviations: BMI, body mass index; PNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SINET, small intestinal neuroendocrine tumour.

3 | RESULTS

3.1 | Improved HRQoL during PRRT

The majority of the patients were men ($n = 134$, 66%), and median age 64 years (range 18–85). Between PRRT cycles 1 and 4, several aspects of the patients' self-reported HRQoL improved (Table 2). The QLQ-C30 assessment showed improvement in global quality of life together with role and emotional functioning, and symptom relief was achieved concerning fatigue, nausea/vomiting, pain, insomnia, appetite loss, and diarrhoea. Using the more NET-specific QLQ-GINET21, patients improved in social functioning, as well as in the following symptoms; endocrine symptoms (flushing, night sweats), gastrointestinal symptoms, treatment-related symptoms, disease-related worries, and weight loss. For the subgroup of SINET patients ($n = 124$), improvement was detected in several categories, presented in Table 3. For patients with PNETs ($n = 45$), only role functioning, fatigue, social functioning, gastrointestinal symptoms, and weight loss were improved (Table S1a), and these patients experienced an increase in endocrine symptoms. In the subgroup of patients with "other NETs" ($n = 35$), improvement was seen in several categories (Table S1b). For patients with functioning tumours compared to nonfunctioning tumours, improvements were seen in additional symptoms; nausea/vomiting, appetite loss, diarrhoea, and endocrine and treatment-related symptoms (Tables S3a and S3b). Gender differences were detected at cycle 1 where women ($n = 70$) rated disease related worries worse than men ($n = 134$) ($p < .001$). Men improved in global quality of life, three functioning scales and seven symptoms, compared to women who improved in two functioning scales and five symptoms. These differences may be due to a lower number of female patients. In women, several other symptoms differed clinically between cycles 1 and 4 (mean score differences were ≥5) but did not reach statistical significance (data not shown).

3.2 | Less improvements in patients with overweight

A total of 94 patients (46%) were overweight (BMI >25), and 22 patients (11%) were obese (BMI >30) when starting PRRT. Patients who were a normal weight (BMI <25) improved in more HRQoL aspects, such as social functioning, nausea/vomiting, pain, diarrhoea, and treatment-related symptoms (Table S2a) than the overweight patients (Table S2b). A minor decrease in BMI was detected between cycles 1 and 4 ($p < .01$) in approximately half of the patients ($n = 107$).

3.3 | Less improvements in older patients

Patients younger than 65 ($n = 107$, 65% functioning tumours) reported improvement in global quality of life, role and emotional functioning, fatigue, nausea/vomiting, pain, insomnia, appetite loss, and diarrhoea during the treatment, whereas older patients

TABLE 2 HRQoL before PRRT cycles 1 and 4 in all patients with NETs ($n = 204$).

HRQoL aspect	Mean scores (SD)				Mean difference (SD)	
	No.	Cycle 1	No.	Cycle 4	Cycle 1–4	*p*-value
EORTC QLQ-C30						
Global quality of life	201	64 (21)	204	70 (20)	6 (19)	<.0001
Functional scales						
Physical	204	81 (18)	204	84 (17)	3 (15)	
Role	200	72 (28)	204	80 (25)	8 (25)	<.0001
Emotional	201	77 (20)	204	82 (19)	5 (17)	<.0001
Cognitive	202	86 (17)	204	88 (16)	2 (16)	
Social	201	75 (24)	204	79 (22)	4 (24)	
Symptom scales						
Fatigue	202	34 (24)	204	29 (23)	−5 (21)	<.001
Nausea/vomiting	203	11 (19)	202	6 (12)	−5 (19)	<.0001
Pain	203	19 (24)	204	14 (20)	−5 (23)	<.01
Dyspnoea	191	18 (24)	201	18 (24)	0 (24)	
Insomnia	203	24 (29)	204	17 (26)	−7 (23)	<.0001
Appetite loss	202	12 (24)	204	7 (18)	−5 (23)	<.01
Constipation	202	10 (21)	203	6 (17)	−4 (20)	
Diarrhoea	201	31 (33)	201	25 (29)	−6 (29)	<.01
Financial difficulties	200	14 (25)	204	13 (26)	−1 (24)	
EORTC QLQ-GINET21						
Functional scales						
Social	196	68 (22)	201	73 (21)	5 (19)	<.0001
Information	194	85 (25)	198	82 (26)	−3 (29)	
Sexual functioning	136	66 (35)	145	69 (34)	3 (26)	
Symptom scales						
Endocrine	196	18 (20)	201	13 (17)	−5 (20)	<.001
Gastrointestinal	195	22 (16)	201	17 (15)	−5 (16)	<.0001
Treatment related	105	15 (19)	178	9 (15)	−5 (21)	<.05
Disease-related worries	196	39 (26)	200	33 (25)	−6 (22)	<.0001
Weight loss	196	20 (31)	201	10 (23)	−10 (29)	<.0001
Weight gain	195	6 (19)	200	9 (18)	3 (20)	
Muscle and/or body pain	194	21 (26)	200	21 (27)	0 (28)	

Note: Where mean scores differed clinically relevantly by ≥5 points, Wilcoxon signed-rank test was used to test for statistical significance.

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; GINET21, Gastrointestinal Neuroendocrine Tumour Cancer-Specific Module; HRQoL, health-related quality of life; PRRT, peptide receptor radionuclide therapy; SD, standard deviation.

(>65 years, $n = 97$, 67% functioning tumours) reported improvement only in role functioning and insomnia (data not shown).

3.4 | HRQoL in NET patients compared to reference population

At the start of PRRT, patients with NETs experienced lower quality of life and rated all functional abilities lower than the reference population, with the exception of cognitive functioning. Patients with NETs also rated all their symptoms worse, except pain and dyspnoea. At the time of PRRT cycle 4, the patients had improved in several aspects and rated emotional functioning at the same level as the reference population (Table 4).

4 | DISCUSSION

In this study, HRQoL evaluation in patients with NETs during PRRT showed an improvement in global quality of life, role and emotional

TABLE 3 HRQoL before PRRT cycles 1 and 4 in patients with SINETs ($n = 124$).

HRQoL aspect	Mean scores (SD)				Mean difference (SD)	
	No.	Cycle 1	No.	Cycle 4	Cycle 1–4	*p*-value
EORTC QLQ-C30						
Global quality of life	122	64 (21)	124	70 (20)	6 (20)	<.01
Functional scales						
Physical	124	81 (18)	124	83 (19)	2 (16)	
Role	122	72 (27)	124	79 (25)	7 (27)	<.01
Emotional	122	77 (21)	124	83 (18)	6 (18)	<.001
Cognitive	123	85 (18)	124	88 (17)	3 (18)	
Social	122	75 (25)	124	79 (22)	4 (25)	
Symptom scales						
Fatigue	124	33 (24)	124	30 (23)	−3 (22)	
Nausea/vomiting	124	12 (19)	123	7 (13)	−5 (19)	<.01
Pain	124	20 (24)	124	15 (21)	−5 (23)	<.05
Dyspnoea	115	17 (23)	122	19 (26)	2 (26)	
Insomnia	124	24 (30)	124	19 (26)	−5 (22)	<.01
Appetite loss	123	11 (23)	124	8 (19)	−3 (21)	
Constipation	123	7 (19)	124	6 (16)	−1 (20)	
Diarrhoea	123	41 (34)	123	33 (29)	−8 (30)	<.01
Financial difficulties	121	13 (25)	124	13 (26)	0 (27)	
EORTC QLQ-GINET21						
Functional scales						
Social	121	69 (22)	123	74 (22)	−5 (19)	<.05
Information	119	84 (26)	123	80 (26)	−4 (27)	
Sexual functioning	80	69 (35)	90	71 (34)	2 (27)	
Symptom scales						
Endocrine	121	22 (21)	123	15 (18)	−7 (21)	<.0001
Gastrointestinal	120	24 (16)	123	18 (15)	−6 (16)	<.0001
Treatment related	72	15 (19)	111	8 (14)	- 7 (19)	<.05
Disease-related worries	121	36 (26)	122	33 (24)	−3 (21)	
Weight loss	121	20 (32)	123	11 (26)	−9 (30)	<.001
Weight gain	120	3 (12)	122	7 (15)	4 (15)	
Muscle and/or body pain	120	24 (27)	122	20 (27)	−4 (28)	

Note: Where mean scores differed clinically relevantly by ≥5 points, Wilcoxon signed-rank test was used to test for statistical significance.

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; GINET21, Gastrointestinal Neuroendocrine Tumour Cancer-Specific Module; HRQoL, health-related quality of life; PRRT, peptide receptor radionuclide therapy; SD, standard deviation; SINET, small intestinal neuroendocrine tumour.

functioning together with relief of multiple symptoms, from the initiation of the treatment to the last PRRT cycle. These results are in concordance with those of a phase II study by Khan et al.[20] Also, in line with previous reports,[11,21] the patients with SINET in our study experienced a reduction in several symptoms together with improved role, emotional and social functioning. Our study demonstrated several aspects of improved HRQoL, contrary to Martini et al.[13] who found overall stable and nonresponsive HRQoL during PRRT in a small cohort of patients with SINETs and PNETs. Although, consistent with this study,[13] we found that patients with PNETs reported less improvement compared to those with SINETs and other NET types.

The QLQ-GINET21 questionnaire provides more precise measurements of HRQoL than the QLQ-C30 regarding NET-specific symptoms. In concordance with our results, only one study[21] has previously used data from the QLQ-GINET21 questionnaire and demonstrated improvement in HRQoL during PRRT for patients with SINETs. In our study, this questionnaire, for patients with SINETs, PNETs, and other NETs, detected improvements in social functioning,

TABLE 4 HRQoL in reference population and in patients with NETs before PRRT cycles 1 and 4.

HRQoL aspect	Mean scores (SD)						Mean difference (SD)		Mean difference (SD)	
	No. Ref.	Ref. population	No. NET	Cycle 1	No. NET	Cycle 4	Ref. pop-Cycle 1	*p*-value	Ref. pop-Cycle 4	*p*-value
EORTC QLQ-C30										
Global quality of life	201	76 (9)	204	64 (21)	204	70 (20)	12 (23)	<.0001	6 (22)	<.0001
Functional scales										
Physical	204	89 (9)	204	81 (18)	204	84 (17)	8 (19)	<.0001	5 (19)	<.0001
Role	200	89 (9)	204	72 (28)	204	80 (25)	17 (29)	<.0001	9 (26)	<.0001
Emotional	201	86 (7)	204	78 (20)	204	82 (19)	8 (22)	<.0001	4 (20)	
Cognitive	202	88 (6)	204	86 (17)	204	88 (16)	2 (18)		0 (17)	
Social	201	91 (6)	204	75 (24)	204	79 (22)	16 (25)	<.0001	12 (23)	<.0001
Symptom scales										
Fatigue	202	19 (9)	204	33 (24)	204	29 (23)	−14 (25)	<.0001	−10 (24)	<.0001
Nausea/vomiting	203	3 (3)	204	11 (19)	202	6 (12)	−8 (17)	<.0001	−3 (12)	
Pain	203	20 (14)	204	19 (24)	204	14 (20)	1 (27)		6 (25)	<.01
Dyspnoea	191	15 (8)	204	18 (24)	201	18 (24)	−3 (25)		−3 (26)	
Insomnia	203	18 (9)	204	24 (29)	204	17 (26)	−6 (31)	<.01	1 (27)	
Appetite loss	202	3 (3)	204	12 (24)	204	7 (18)	−9 (24)	<.0001	−4 (18)	
Constipation	202	5 (4)	204	10 (21)	203	6 (17)	−5 (21)	<.01	−1 (18)	
Diarrhoea	201	6 (5)	204	31 (33)	201	25 (29)	−25 (33)	<.0001	−19 (29)	<.0001
Financial difficulties	200	5 (6)	204	14 (25)	204	13 (26)	−9 (26)	<.0001	−8 (27)	<.0001

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; HRQoL, health-related quality of life; PRRT, peptide receptor radionuclide therapy; SD, standard deviation.

in endocrine, gastrointestinal and treatment-related symptoms, and with reduced disease-related worries and weight loss.

Our study is the first to report that patients with NETs and with overweight report a lower HRQoL than those of normal weight. Thus, treatment did not improve the condition for patients with overweight to the same extent as those with a normal BMI. Obesity is per se associated with lower estimated quality of life,[22] and the effect of PRRT on HRQoL needs further exploration in patients with overweight and obesity.

HRQoL did not improve in patients older than 65 to the same extent as younger patients (<65 years old). The general population (70–79 years) without a cancer diagnosis experiences lower levels of physical and role functioning, and scores higher for several symptoms than younger individuals (<70 years old).[17] This is likely due to impaired body functions and more comorbidities in the elderly. Milanetto et al.[10] also found lower HRQoL in older patients with SINETs compared to those younger than 65. Thus, health care professionals should be aware that older patients with NETs may have other challenging care needs than the young during PRRT.

For all questionnaire items, except for cognitive functioning, pain and dyspnoea, patients with NETs rated their HRQoL at the start of PRRT lower than the reference population. This was anticipated as PRRT is generally offered to patients with advanced disease. It is important to enable patients to make an informed decision about treatments offered, not only present biological effects without including effects on HRQoL,[7] and these results may be used to increasing patient participation and person-centred care.

Strengths of the current study are validated questionnaires measuring HRQoL both generally and tumour specific, and also the comparison against a matched normal population. One limitation of our study was the lack of nonresponse analyses, as patients with deteriorating health may be unable to fill in the questionnaires. Another confounder may have been not analysing HRQoL in patients who received less than four cycles of PRRT, together with reasons for ending therapy early.

5 | CONCLUSIONS

This study shows that PRRT improves several aspects of HRQoL. Global quality of life, role, and emotional functioning improved together with relief of multiple symptoms. Potential risks for less HRQoL are patients with overweight and old age (>65 years). Further HRQoL studies in subgroups of patients with different NET types, and qualitative research methods, are necessary to improve our understanding of the disease burden and to improve person-centred care.

AUTHOR CONTRIBUTIONS

Katarina Edfeldt: Data curation; formal analysis; project administration; writing – original draft. **Per Hellman:** Conceptualization; supervision; writing – review and editing. **Dan Granberg:** Investigation; supervision; writing – review and editing. **Pernilla Lagergren:** Formal analysis;

writing – review and editing. **Espen Thiis-Evensen:** Methodology; writing – review and editing. **Anders Sundin:** Investigation; methodology; supervision; writing – review and editing. **Camilla Andersson:** Data curation; formal analysis; investigation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Regional Ethics Committee in Uppsala, Sweden (Dnr.2010/177) and written informed consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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