Quality of Life in 265 Patients with Gastroenteropancreatic or Bronchial Neuroendocrine Tumors Treated with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

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Quality of life (QOL) is an important outcome in cancer therapy. In this study, we investigated the QOL and symptoms after [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) therapy in patients with inoperable or metastasized gastroenteropancreatic or bronchial neuroendocrine tumors (NETs). **Methods:** Two hundred sixty-five Dutch patients completed the QOL questionnaire of the European Organization for the Research and Treatment of Cancer after being treated for NETs. ANOVA was used for statistical analyses, with a *P* value of 0.05 or less being considered significant. Differences of at least 10 points in global health status (GHS)/QOL scores, symptom scores, and Karnofsky performance scores (KPS) before and after therapy were regarded as indicating an improvement. **Results:** Regardless of the treatment outcome, GHS/QOL, insomnia, appetite loss, and diarrhea improved significantly in the total group. These improvements were also seen in patients with bone metastases or a decrease of 50% or more in chromogranin A. Improvement in the scores by at least 10 points was also analyzed in a subgroup of patients with decreased GHS/QOL or symptoms at the start of therapy: in 36% of these patients, GHS/QOL improved after therapy; in 49%, fatigue; in 70%, nausea plus vomiting; in 53%, pain; in 44%, dyspnea; in 59%, insomnia; in 63%, appetite loss; in 60%, constipation; and in 67%, diarrhea. Additionally, we did not see a statistically significant deterioration in patients who had GHS/QOL 100, KPS 100, or no symptoms at the start. In patients with initial stable disease or remission after treatment, GHS/QOL and KPS decreased significantly when regrowth of the tumors occurred. **Conclusion:** GHS/QOL, KPS, and symptoms improved significantly after ^{177}Lu-octreotate therapy, and there was no significant decrease in QOL in patients who had no symptoms before therapy. In patients who had suboptimal scores for GHS/QOL or symptoms before therapy, a clinically significant improvement was demonstrated. Our results indicate that ^{177}Lu-octreotate therapy not only reduces tumors and prolongs overall survival but also improves the patients' self-assessed QOL.

Key Words: gastroenteropancreatic neuroendocrine tumor; bronchial neuroendocrine tumor; quality of life; health-related quality of life; peptide receptor radionuclide therapy; [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

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Gastroenteropancreatic and bronchial neuroendocrine tumors (NETs) are relatively rare neoplasms that derive from the neuroendocrine system. The incidence is 1–2.5 per 100,000 individuals (*1–6*). Because they often have an unpredictable biologic behavior, the time to the final diagnosis is frequently delayed (*2*). The only potentially curative treatment is surgery (*2*). However, several studies have shown that a large group of patients already has nonlocalized disease at diagnosis (*5,7*). Compared with other malignancies, NETs grow relatively slowly, and life expectancy is relatively long (*8*). For patients with inoperable or metastasized disease, antiproliferative therapies are limited. Classic chemotherapeutic agents are not suitable, although in a subgroup of patients with pancreatic NETs, objective responses were achieved after therapy with streptozocin- or temozolomide-based regimens (*9–12*). Because of the highly vascular nature of these tumors, treatment with angiogenesis inhibitors such as sunitinib (Sutent; Pfizer) has recently gained more interest (*13*).

Additionally, mammalian-target-of-rapamycin inhibitors are being investigated in phase II and III trials for controlling tumor growth in NETs (*14–16*).

Treatment with somatostatin analogs (SSA), interferon-α, or the combination can reduce symptoms due to hormone overproduction in patients with NETs, but tumor reduction is achieved in only a small percentage of patients (*17–20*). However, in a recently published study, Rinke et al. (*17*) reported a longer median time to progression in patients using octreotide long-acting release (Sandostatin LAR; Novartis), compared with controls.

Liver metastases can be treated with local ablative nonsystemic therapies such as radiofrequency ablation, embolization with or without chemotherapeutic agents, or

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radionuclide-loaded microspheres, and surgical resection may also be used for cytoreductive purposes (*21*). Liver transplantation may not be of benefit in extrahepatic metastasized disease, although controversy exists as to its actual use (*22*).

A recently developed therapy for the management of inoperable and metastasized NETs is peptide receptor radionuclide therapy (PRRT) with, for example, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) (*23–25*). Treatment with ^{177}Lu-octreotate has been shown to be relatively safe, and most patients have had remission or stable disease after the therapy (*24*).

Self-reported quality of life (QOL) is also regarded as an important outcome for the effect of a therapy in patients with malignant diseases: improvement in health-related QOL is one of the potential benefits that are considered by the United States Food and Drug Administration for the approval of new anticancer drugs (*26*).

A limited amount of research has been published about QOL in patients with NETs (*27–29*). A report on QOL after ^{177}Lu-octreotate in 50 patients with NETs was published by Teunissen et al. in 2004 (*30*). In that study, a statistically significant improvement in the global health status (GHS)/QOL was observed after treatment with ^{177}Lu-octreotate ($P < 0.01$).

In the present study, a larger group of patients treated with ^{177}Lu-octreotate was analyzed. Additionally, the relationship between tumor response and changes in QOL was analyzed in a patient-based manner.

MATERIALS AND METHODS

Study Design

Two hundred eighty-two Dutch patients were treated with ^{177}Lu-octreotate at our center at Erasmus MC from 2000 until 2007 according to the protocol of a phase II single-arm study. Two hundred twenty-six foreign patients were not included in this study, because of incomplete follow-up data.

The most important inclusion criteria for therapy were histologically proven metastatic or inoperable NETs, tumor uptake at least equal to liver uptake on ^{111}In-pentetreotide (OctreoScan; Covidien) scans, Karnofsky performance score (KPS) of at least 50, creatinine clearance of at least 40 mL/min, a platelet level of at least $80 \cdot 10^9$/L, a hemoglobin level of at least 9.7 g/dL, and a white blood cell count of at least $2.0 \cdot 10^9$/L.

Outcome Measures

The follow-up visits were scheduled at fixed time points: 6 wk, 3 mo, and 6 mo after therapy with ^{177}Lu-octreotate and biannually thereafter. At these visits, blood was drawn for analysis; patients also underwent CT or MRI. KPS was scored at baseline by the physician and at follow-up by the nurses. Additionally, at these visits and before therapy, patients completed the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)–core module (C30), a questionnaire developed to assess the quality of life of cancer patients. The EORTC QLQ-C30 has 30 items. Twelve items are fitted in 8 symptom scales, which are fatigue, nausea plus vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea. An additional item, financial difficulties, was not analyzed in this study. Five items are fitted into functional scales comprising physical functioning, emotional functioning, role functioning, cognitive functioning, and social functioning. Two remaining items give the score of GHS/QOL, which provides information on the overall experience of QOL and is therefore regarded as the most important scale to study (*31*).

The EORTC QLQ-C30 is a sensitive instrument for measuring changes in patients' performance status (*32*).

Timing and Data Collection

At the first visit after receiving therapy, the patients were unaware of their tumor response. In this study, the questionnaires that were completed at that visit were compared with those completed at baseline. For analyses and calculations, at least 2 questionnaires were necessary. Thus, patients who completed only 1 questionnaire were not included in this study.

Missing Data

Although all patients were instructed on how to complete the questionnaires, and although the questionnaires were carefully collected, there were still some missing items, which were handled as described in the EORTC guidelines for the QOL assessment (*33*).

Data Analysis

According to the instructions of the EORTC QOL study group, the EORTC QLQ-C30 scores were transformed to 0–100 scales (*33*). In this study, ANOVA was used to compare patients' scores before ^{177}Lu-octreotate treatment with patients' scores after treatment; a P value of 0.05 or less was considered significant.

Another analysis was done to study whether changes in scores were indeed of clinical interest. GHS/QOL, KPS, and function scales range from 0 to 100, with a higher score representing a higher level of functioning. Symptom scores range from 0 to 100, with a higher score representing more symptoms. Osoba et al. have shown that a change of at least 10 points is of clinical importance (*34*). This difference of 10 points in scores was used to calculate the percentages of patients who had a clinically important improvement. These patient-based calculations were done only with scores for GHS/QOL and symptoms. Additionally, an improvement of 10 points in KPS, a weight gain of 3 kg or more, and a 50% lower plasma chromogranin-A (CgA) level after therapy at the first follow-up visit were considered to represent clinical or biochemical improvement.

Before each course of ^{177}Lu-octreotate, all patients who used SSA were instructed to discontinue this medication according to protocol; the medication was resumed after each course. We separately analyzed patients who scored diarrhea in the questionnaire and used SSA or antidiarrheic medication and patients who had diarrhea and did not use medication. Patients who had uncontrollable hormone-induced symptoms did not stop SSA use during PRRT.

At baseline, 6 wk, and 3 mo after PRRT, CT and MRI were performed to categorize tumor response into 3 groups following the modified Southwest Oncology Group solid tumor response criteria: a remission group, which included tumor reduction of more than 25%; a stable disease group; and a progressive disease group (*35*).

RESULTS

Seventeen of the 282 patients were excluded from this study, for several reasons: 1 patient had a developing

cognitive impairment; 3 patients did not fill out a baseline questionnaire; 3 patients had missing forms; 2 patients received less than 22.2 GBq because of thrombocytopenia and 1 patient received 18.5 GBq because of achieving the maximum dose, which was calculated with kidney dosimetry; 2 patients were lost to follow-up; and 5 patients had progressive disease after 1 cycle and did not fill out a second questionnaire, which is needed for comparison. Because of progressive disease, 24 patients did not reach the therapeutic doses of 22.2–29.6 GBq but were included in this study because they filled out at least 2 questionnaires during the treatment. Thus, we analyzed a total of 265 patients in this study, 241 of whom completed the whole treatment and received 22.2–29.6 GBq of ^{177}Lu-octreotate and whose baseline questionnaires were compared with questionnaires completed at the first visit after completion of therapy. The baseline characteristics of the 265 patients are summarized in Table 1.

TABLE 1
Baseline Characteristics

Characteristic	No. of patients	Percentage
Total	265	
Sex		
Female	128	48
Male	137	52
KPS		
Mean	89.0	
Median	90	
Range	50–100	
Type of tumor		
Carcinoid	169	64
Nonfunctioning NET, pancreas	60	23
NET, unknown origin	25	9
Gastrinoma	3	1
Glucagonoma	1	0.4
Insulinoma	5	2
VIPoma	2	1
Metastases		
Liver	179	68
Bone	8	3
Liver and bone	48	18
None	30	11
Prior anticancer therapy		
Surgery	47	18
Chemotherapy	23	9
Radiotherapy	12	5
SSA	164	62
Progressive disease before therapy		
Yes	128	48
No	51	19
Unknown	86	32
Tumor response groups		
Remission	118	45
Stable disease	94	35
Progressive disease	38	14
Unknown response outcome	15	6

Mean age was 58.5 y, with a range of 23–83 y.

QLQ scores at baseline were compared with scores after ^{177}Lu-octreotate therapy in 4 groups: the total group, the group with remission, the group with stable disease, and the group with progressive disease. Physical functioning, role functioning, and cognitive functioning did not change significantly after therapy. Before therapy, the mean score for GHS/QOL was 54.0 in the progressive disease group and 70.0 in the stable disease and remission groups.

In the total group, regardless of treatment outcome, GHS/QOL, emotional and social functioning, insomnia, appetite loss, and diarrhea improved significantly (Fig. 1). In the group of patients who had remission, KPS and fatigue also improved significantly (Fig. 1).

Only 4.5% (12/265) of the patients scored no symptoms or GHS/QOL 100 at baseline. All other patients scored either GHS/QOL less than 100 or symptom score more than 0.

Figure 2 shows what percentage of patients who had GHS/QOL 100 or no symptoms before therapy had a clinically significant deterioration of at least 10 points after therapy. A separate analysis (ANOVA) in patients with no symptoms, GHS/QOL 100, or KPS 100 at baseline showed that there was no statistically significant deterioration in these patients after therapy.

Clinically significant improvement in the symptom scales by at least 10 points was also demonstrated with patient-based calculations in the subgroup of patients who had symptoms with decreased GHS/QOL or symptoms at the start of therapy (n = 265 in Fig. 3): in 36% of these patients, GHS/QOL improved after therapy; in 49%, fatigue; in 70%, nausea plus vomiting; in 53%, pain; in 44%, dyspnea; in 59%, insomnia; in 63%, appetite loss; in 60%, constipation; and in 67%, diarrhea (Fig. 3). In the outcome groups, symptoms significantly improved in 38%–90% of the patients within the different subgroups who had a specific symptom before therapy. This analysis was performed separately for each outcome group (Fig. 3). Additionally, KPS, weight, CgA, and GHS/QOL improved in 14%–60% of the patients in the different outcome groups (Fig. 4). Patients with unknown treatment outcome—tumor response not measurable—were included in the total group for analysis of GHS/QOL and symptom score but were not included in the graphs as a group.

For the 154 patients who had scored pain in the questionnaires before therapy, and for the 129 patients who had scored diarrhea, separate analyses of the symptom scales for pain and diarrhea, respectively, were performed. Seventy-two of 154 patients (47%) used pain medication before therapy, and 82 (53%) did not use medication. Sixty-one of 123 patients (50%) who had no change in the dose of pain medication—including patients who did not use any medication at all—scored a decrease in pain after therapy (Fig. 5). Twenty of 26 patients (77%) in the group that had a decrease in the dose of pain medication also scored a decrease in pain,

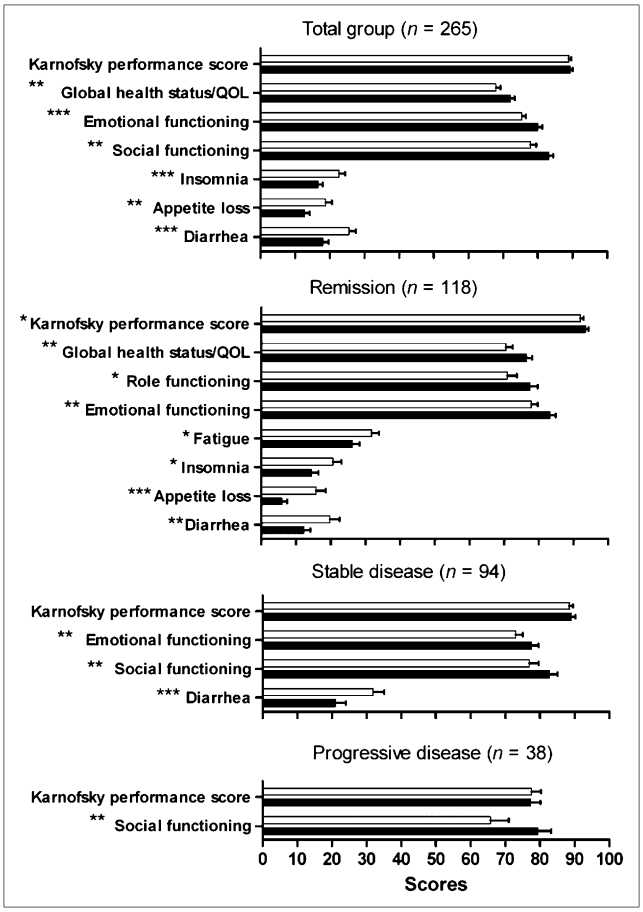

FIGURE 1. Mean scale scores of EORTC QLQ-C30 and KPS before PRRT (white bars) vs. at 6 wk after therapy (black bars) ± SD. Only scores that changed significantly are shown, except for KPS. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

whereas none of the 5 patients who had an increased dose of pain medication scored less pain in the questionnaires. In 129 patients with diarrhea, 87 (67%) used SSA or antidiarrheic medication before therapy and 42 (33%) did not use medication. Seventy-four of 111 patients (67%) who had no change in the dose of SSA or antidiarrheic medication—including patients who did not use any medication at all—scored a decrease in diarrhea after therapy. Nine of 11 patients (82%) who had a decrease in the dose of SSA or antidiarrheic medication also scored a decrease in diarrhea. Three of 7 patients (43%) in the group who had an increase in the dose of SSA or antidiarrheic medication scored less diarrhea in the questionnaires (Fig. 5). In addition, we analyzed urinary 5-hydroxyindoleacetic acid levels in patients who had diarrhea before therapy. Sixty-two of 129 patients who had diarrhea before therapy (48%) had complete data for comparison. Twelve of 62 (19%) had a decrease of at least 50% in 5-hydroxyindoleacetic acid levels, without a change in SSA dose.

The results of ANOVA for patients who had bone metastases at baseline, no metastases at baseline, or decreases of 50% or more in CgA levels are shown in Figure 6.

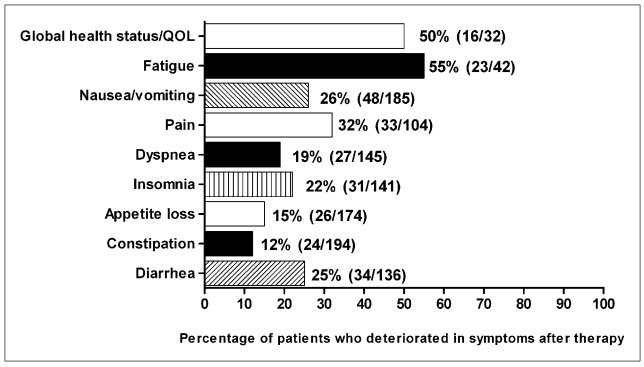

FIGURE 2. Clinically significant deterioration in GHS/QOL or symptoms in patients who had GHS/QOL 100 or no symptoms before PRRT. Numbers of patients are in parentheses.

We also analyzed the change in GHS/QOL, weight, and KPS when patients developed progressive disease after initial remission or stable disease after PRRT. This analysis was performed on 48 patients: GHS/QOL improved initially after therapy but deteriorated when the disease was progressive after the initial response after PRRT (ANOVA, $P \leq 0.01$). The same pattern was demonstrated for KPS (ANOVA, $P \leq 0.001$). Weight, however, did not deteriorate significantly at that moment, unlike GHS/QOL and KPS, although it did improve significantly after PRRT (Fig. 7).

DISCUSSION

When patients with NETs present with symptoms, they are usually obstructive symptoms due to mass effects of the tumor or are hormone-induced symptoms. Obstructive symptoms in patients with NETs are mostly pain, nausea, or vomiting. Hormone-induced symptoms common in patients with NETs are diarrhea or flushing. Fatigue and insomnia occur frequently in cancer patients. However, patients with NETs may also be asymptomatic at the time of diagnosis or have a relatively good health-related QOL at baseline, as reported in other studies (*27,29,30*). This is also observed in our patient group. However, patients who had progressive disease during or after therapy, that is, patients who had progressive disease during the course of the treatment, started with a lower GHS/QOL.

We found that KPS and 8 of the 15 scales of the EORTC QLQ-C30—GHS/QOL, role functioning, emotional functioning, social functioning, fatigue, insomnia, appetite loss, and diarrhea—improved significantly after ^{177}Lu-octreotate therapy, even though a large proportion of patients already used SSA (62%). Results of patient-based calculations demonstrated a clinically important improvement in GHS/QOL, all symptom scales, KPS, and weight, as well as biochemical improvement, in the group of patients who had remission. In the stable disease and progressive disease groups, these improvements occurred less frequently. The most important improvements, such as for diarrhea, pain, nausea, and vomiting, were observed in patients who had

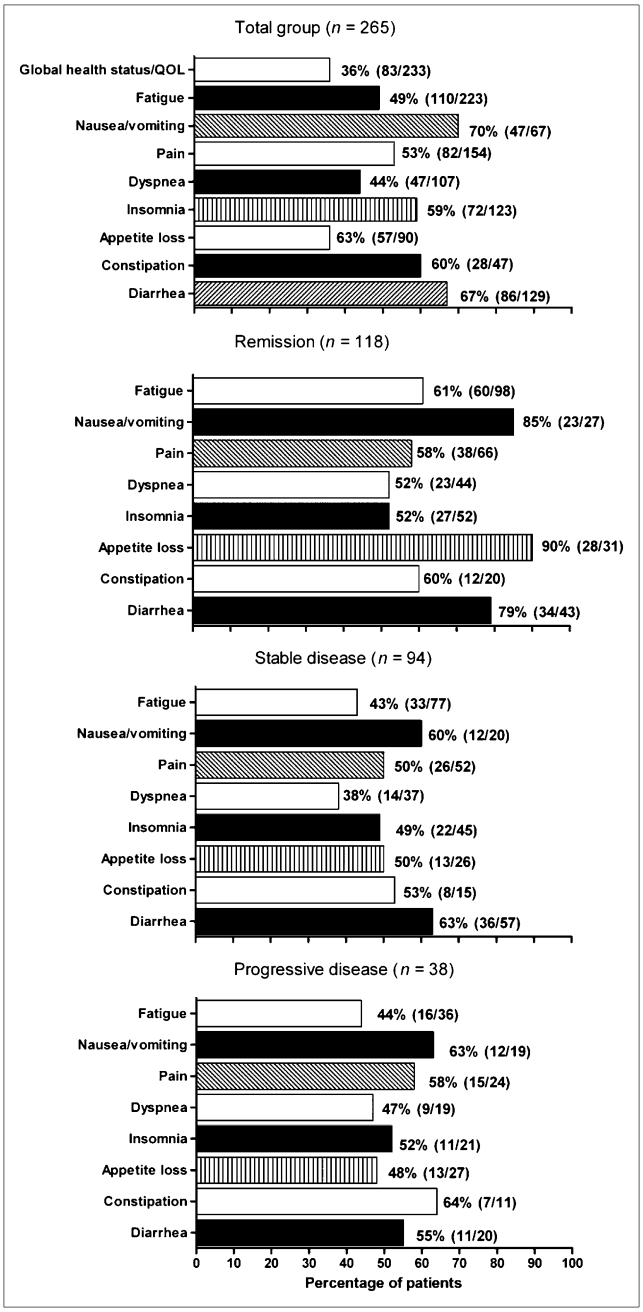

FIGURE 3. Improvement in symptoms in patients who had symptoms before PRRT with score of at least 10 points less, which is clinically relevant. Numbers of patients are in parentheses.

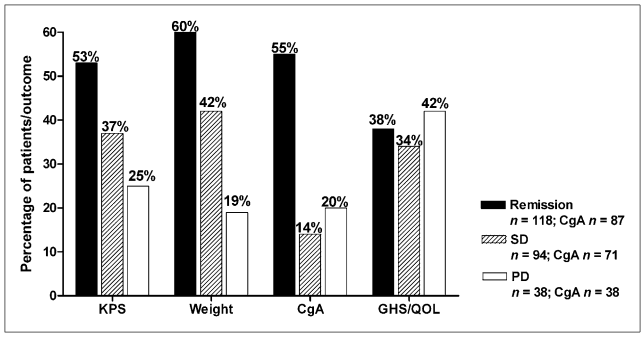

FIGURE 4. Percentages of patients per outcome group who had improved KPS, weight, CgA, and GHS/QOL. Increase of 10 points or more in KPS or GHS/QOL after PRRT in patients who had scores of less than 100 was regarded as clinically important improvement, as was weight gain of 3 kg in patients who had weight loss of 3 kg or more before PRRT. Fifty percent lower CgA plasma level after PRRT was regarded as biochemical improvement in patients who had elevated plasma CgA concentrations before PRRT. PD = progressive disease; SD = stable disease.

tumor regression after therapy with ^{177}Lu-octreotate, that is, concordant with the tumor response, strongly suggesting that the improvement was a direct result of treatment with ^{177}Lu-octreotate. The statistically significant improvements were also shown in patients with bone metastases at baseline and with a decrease of CgA levels after therapy. To find out if this was entirely the result of ^{177}Lu-octreotate treatment, we analyzed the use of pain medication, SSA, or antidiarrheic medication before, during, and after therapy. Our results imply that a decrease in pain and diarrhea is most probably a result of ^{177}Lu-octreotate therapy, because both pain and diarrhea were reduced in a subgroup of patients who either did not use medication or had had no change in the dose or used less medication after therapy.

Improvements in KPS and weight, tumor markers, and symptom scores were also seen in patients who had stable disease or progressive disease as the outcome after therapy but were seen less frequently than in the group with remission, except for GHS/QOL and constipation, which improved more often in the progressive disease group. Although GHS/QOL improved to a statistically significant degree in the remission group, the most frequent clinically important improvement in GHS/QOL was demonstrated in the progressive disease group—a finding that was not entirely as expected. Although we cannot draw firm conclusions without a control group, these results may indicate an effect of being treated rather than a therapeutic effect: patients in the progressive disease group more often had advanced disease and a significantly lower GHS/QOL at the start than did the other patients. Thus, most were treated at a point at which there seemed to be no other treatment option, and their expectations may therefore have been higher. These results imply that improvement in GHS/QOL in the progressive disease group may be a result of being treated rather than an effect of the therapy.

The biochemical improvement in patients with stable disease, together with clinically important improvement in GHS/QOL, KPS, and weight, cannot be explained by the tumor response on CT or MRI.

These findings in patients with stable disease and progressive disease imply that there are limitations in the use of anatomic imaging and biomarkers such as CgA in NET patients, especially in patients with poorly differentiated NETs, underlining the importance of assessing proliferation indexes such as Ki-67, which was unfortunately not routinely available in our study. In these patients,

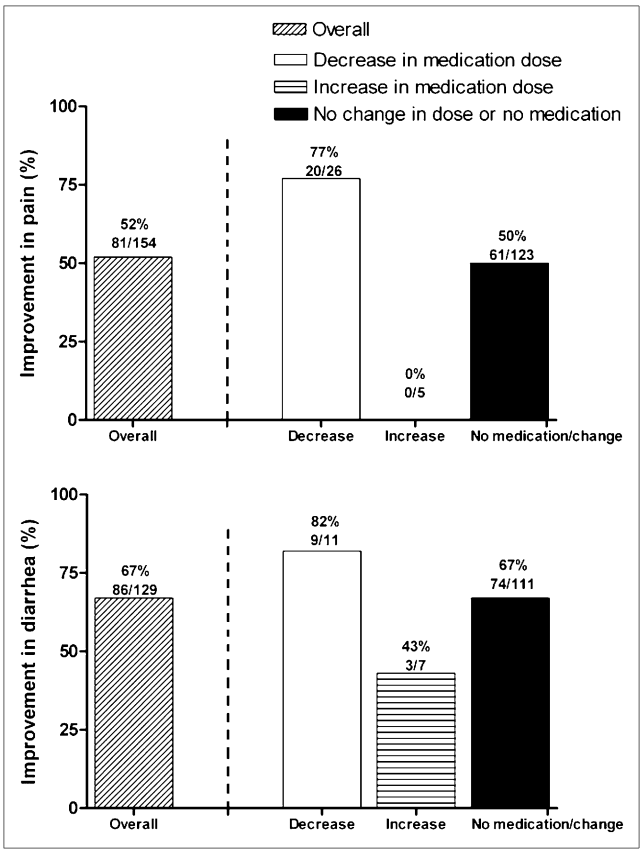

FIGURE 5. Percentages of patients who reported improvement in pain and diarrhea score after PRRT. Dotted bars show percentages of all patients with symptom improvement.

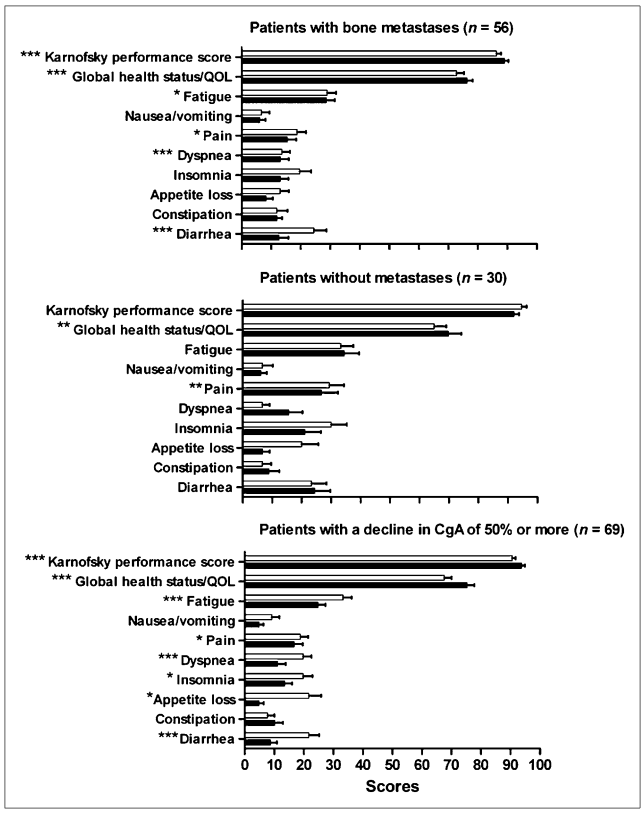

FIGURE 6. Mean scale scores of EORTC QLQ-C30 and KPS before PRRT (white bars) vs. at 6 wk after therapy (black bars) ± SD. Only GHS/QOL and symptoms scores are shown. $^{*}P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$.

functional instead of morphologic imaging may better show changes in tumor activity. Somatostatin receptor scintigraphy or imaging with a metabolic tracer of NETs, such as ^{18}F-DOPA PET (*36*), are such methods for functional imaging. Binderup et al. reported in a recent study (*37*) that ^{18}F-FDG PET had the highest sensitivity for poorly differentiated NETs with a high proliferation rate, a Ki-67 of at least 15%, and negative somatostatin receptor scintigraphy findings, indicating that ^{18}F-FDG PET may be of diagnostic value in such cases. In another recent study (*38*), Ezziddin et al. investigated the role of the Ki-67 proliferation index in predicting the efficacy of PRRT in NET patients and found that Ki-67 indices of up to 20% have no discernible negative effect on response to PRRT. In contrast, they found disappointing outcomes in poorly differentiated NETs, which tend to fail to respond to PRRT even when they display avid receptor-mediated tracer uptake, aiding the view that assessment of Ki-67 is valuable not only for diagnostic purposes but also for therapeutic purposes.

A significant increase followed by a decrease in GHS/QOL and KPS in patients with progression after an initial response of remission or at least stable disease after therapy with ^{177}Lu-octreotate indicates that deterioration and improvement in GHS/QOL or KPS may be a good predictor of response for progressive disease, remission, and perhaps even stable disease. This is in line with reports that have indicated that the EORTC QLQ-C30 could be used for predicting survival as well as tumor response (*39,40*).

In summary, the results of this study demonstrate that tumor response and an improvement in health-related QOL are most probably intertwined and that weight might also be a good predictor of the effect of therapy, rather than health-related QOL alone. In addition, weight gain is most probably not just a result of an improvement in diarrhea after ^{177}Lu-octreotate but may also be a result of an improvement in appetite due to tumor mass reduction. The improvement in GHS/QOL and symptoms, KPS, and weight and a biochemical improvement after therapy with ^{177}Lu-octreotate in a large group of patients, as well as no significant deterioration of clinical condition, indicate that treatment with ^{177}Lu-octreotate improves health-related QOL—an important goal in this patient population. In the future, we will be able to do an analysis using the EORTC-QLQ NET21, a questionnaire developed especially for patients with NETs (*28*).

CONCLUSION

A better health-related QOL in cancer patients with incurable disease is an important outcome of cancer

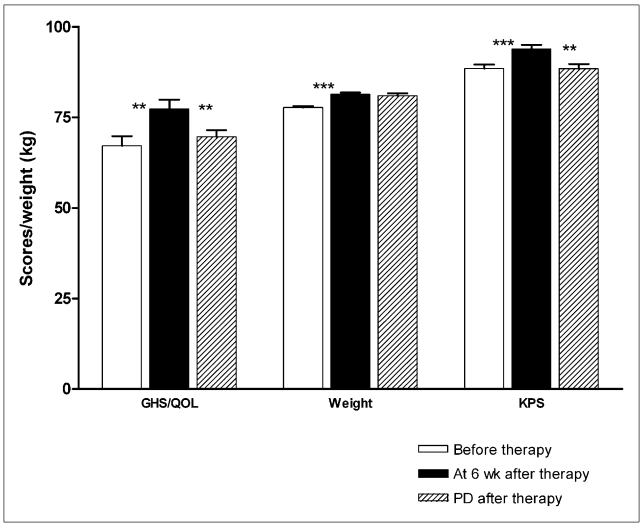

FIGURE 7. GHS/QOL score, weight, and KPS at start of PRRT, after PRRT, and at time of progression in 48 patients who had initially stable disease or remission as treatment outcome after PRRT and in whom tumor progression was observed during follow-up. $^{**}P < 0.01$. $^{***}P < 0.001$.

therapy, especially when survival is prolonged. Moreover, in patients with biologically indolent disease, the aim must be not to deteriorate health-related QOL. This aim requires a treatment that is well tolerated: we reported in 2008 (*24*) that not only was tumor reduction seen in a large group of patients treated with ^{177}Lu-octreotate but also a delayed time to progression and a prolongation of survival, as well as only few adverse effects, defining it as an effective and relatively safe treatment (*24*).

GHS/QOL, KPS, and symptoms improved significantly after ^{177}Lu-octreotate therapy, and there was no significant decrease in QOL in patients who had no symptoms before therapy. In patients who had suboptimal scores for GHS/QOL or symptoms before therapy, a clinically significant improvement was demonstrated.

Our results indicate that ^{177}Lu-octreotate therapy not only reduces tumors and prolongs overall survival but also improves the patients' self-assessed QOL.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No other potential conflict of interest relevant to this article was reported.

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