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ORIGINAL REPORT

Quality of Life in Patients With Gastroenteropancreatic Tumors Treated With [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To evaluate the quality of life (QoL) in patients with metastatic somatostatin receptor positive gastroenteropancreatic tumors treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) therapy.

Patients and Methods
Fifty patients who had been treated with 600 to 800 mCi of ^{177}Lu-octreotate and had a follow-up of at least 3 months were studied. The patients completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 before therapy and at follow-up visit 6 weeks after the last cycle. Overall QoL and specific QoL domains of both the total group of patients and subgroups according to treatment outcome were analyzed. Twenty-four patients had regression, 19 had stable disease, six had progressive disease, and one had nonassessable disease status. Analysis of variance was used for statistical comparison.

Results
A significant improvement in the global health status/QoL scale was observed after therapy with ^{177}Lu-octreotate ($P < .01$). The score increased significantly six weeks after therapy to a mean of 78.2, up from 69.0 (scale range, 0 to 100). Furthermore, significant improvement was observed in the role, emotional, and social function scales. The symptom scores for fatigue, insomnia, and pain were significantly decreased. Patients with proven tumor regression most frequently had an improvement of QoL domains. Unexpectedly, patients with progressive disease also indicated an improvement in their global health/QoL score.

Conclusion
^{177}Lu-octreotate therapy significantly improved the global health/QoL and several function and symptom scales in patients with metastasized gastroenteropancreatic tumors, but especially in those patients with proven tumor regression.

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INTRODUCTION

Neuroendocrine gastroenteropancreatic (GEP) tumors, including pancreatic islet-cell tumors, nonfunctioning neuroendocrine pancreatic tumors, and carcinoids, are relatively rare neoplasms. In comparison with other malignancies, these tumors usually grow slowly.[1] Manifestations of disease in patients are mainly based on symptoms or syndromes caused by the overproduction of bioactive substances or hormones by the tumor, like in carcinoids, gastrinomas, and insulinomas. In nonfunctioning tumors, diagnosis occurs at a relatively late stage of the disease and therefore, widespread metastatic disease is often present. In symptomatic patients, treatment with somatostatin analogs is the therapy of choice and highly effective in these symptoms reduction.[2,3] However, somatostatin analog treatment results in tumor regression in only 4% to 10% of the patients.[4-6]

Peptide receptor radionuclide therapy is a promising treatment modality in patients with metastasized GEP tumors.[7-9] Treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) resulted in a complete remission (CR) in 3%, partial remission (PR) in 35%, stable disease (SD) in 41%, and progressive disease (PD) in 21% of the patients. Also, reported side effects were few.[9] The therapeu-

tic effect on tumor volume is most frequently used as the primary end point in clinical oncologic trials. However, over the last decades, the effect of therapy on the self-reported quality of life (QoL) has also become an important (secondary) end point. To detect subjective differences in aspects of QoL, many assessment instruments have been developed. Most widely used is the European Organization of Research and Therapy in Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), which is especially designed to assess QoL in clinical cancer trials. This questionnaire has been validated and is accepted as a reliable method for the assessment of QoL.[10] Therefore, we chose this questionnaire to evaluate the impact of treatment with ^{177}Lu-octreotate on QoL in patients with metastasized GEP tumors.

PATIENTS AND METHODS

Study Design

Patients were referred from both tertiary care referral centers and community hospitals throughout the country. During the treatment and thereafter, the patients came for follow-up in our hospital. The most important criteria for inclusion were histologically proven metastatic GEP tumor(s) and good tumor uptake on somatostatin receptor scintigraphy. Also, patients had to have a Karnofsky performance status score (KPS) ≥ 50.[9,11] Exclusion criteria were: creatinin clearance < 40 mL/min, platelets $< 80 \times 10^9$/L, hemoglobin < 9.7 g/dL, and WBC count $< 2.0 \times 10^9$/L. A total of 66 patients with metastatic somatostatin receptor positive GEP tumors treated with 600 to 800 mCi ^{177}Lu-octreotate (three to four cycles, 6- to 9-week interval) could be analyzed. Eight patients were excluded because of missing forms at the 6-week follow-up visit. In these cases, the forms were missing because of administrative reasons. Seven patients were excluded because of follow-up outside the Netherlands, and one because of progressive disease. A total of 50 patients were analyzed.

Outcome Measures

QoL was assessed with the EORTC QLQ-C30 (version 3.0), a patient-based questionnaire which includes a total of 30 items and is composed of scales that evaluate physical (five items), emotional (four items), role (two items), cognitive (two items), and social (two items) functioning, as well as global health status (two items). Higher mean scores on these scales represent better functioning. There are also three symptom scales measuring nausea and vomiting (two items), fatigue (three items), and pain (two items), and six single items assessing financial impact and various physical symptoms. A higher mean value on the symptom scales/single items means more symptomatology. Following the scoring instructions given by the EORTC Quality of Life Study group, the raw EORTC QLQ-C30 scores were linearly transformed to 0-100 scales before statistical analyses were performed.[12] A mean change in score between 0 and 5 was regarded as not clinically important. A change in scores between 5 and 10 was regarded as a "little" subjective change, whereas a change between 10 and 20 was regarded as a "moderate" change, and more than 20 was regarded as an "important" change, as previously described.[13] The different outcome groups were defined as regression (including CR, PR, and minimal regression [MR]; 25% to 50% reduction in tumor size), SD, and PD, and were determined by means of computed tomography (CT) and magnetic resonance imaging (MRI) measurements following the WHO solid tumor response criteria. MR was included in the regression group because of the usually slow growth rate of neuroendocrine tumors, if compared with other carcinomas, and because of the cystic lesions that these tumors often cause.

Timing and Data Collection

In accordance with the requirements from the hospital's Ethics Committee, informed consent was obtained from all the patients. Questionnaires were filled out at fixed points in the treatment scheme in the week before the first treatment and at the first follow-up visit 6 weeks after the last treatment. The treating physician scored their KPS. The patients were carefully instructed how to fill out the questionnaire, but were not assisted in answering the questions. At the 6-week follow-up visit, the patients were unaware of the response as the questionnaires were filled out on the same day the first follow-up CT or MRI was performed. Patients were only informed about outcome of therapy at the next follow-up visit when tumor imaging was evaluated. The first questionnaire was used as baseline.

Missing Data

The questionnaires were collected carefully, but some were not filled out adequately and contained missing values at the time of analysis. The missing items were handled with the method of simple mean imputation as described in the Guidelines for assessing QoL in clinical trials provided by the EORTC.[12]

Data Analysis

Analysis of variance (two-sided) was used to compare the patients' ratings before and after treatment. $P < .05$ was considered significant. The linear associations between changes in KPS scores and patients' global health/QoL scores were investigated using Spearman's rank correlation (two-tailed).

RESULTS

Baseline patients' characteristics are listed in Table 1. The questionnaires of 50 patients (mean age, 58 years; range, 30 to 78 years), before and after treatment, were available for analysis. Of the 50 patients, 26 patients (52%) had carcinoid tumor, 13 (26%) neuroendocrine (NE) pancreatic tumor, seven (14%) had NE tumor of unknown origin, three (6%) had gastrinoma, and one (2%) had insulinoma. Twenty-two patients (44%) had been operated in the past, five patients (10%) had received chemotherapy, and 24 patients (48%) had been treated with somatostatin analogs before the ^{177}Lu-octreotate therapy. Seventeen of the included 50 patients (34%) had documented progressive disease within 1 year before the start of therapy. In the other patients, disease was stable for more than 1 year, or progression had not been documented with CT or MRI within the preceding year. Treatment with ^{177}Lu-octreotate resulted in the following responses 3 months after therapy: 24 patients (48%) had tumor regression (CR, PR, and MR), 19 patients (38%) had SD, and six patients (12%) had PD. In one patient, it was not possible to measure tumor response because evidence of disease before and after therapy could only be visualized with somatostatin scintigraphy.

Table 1. Baseline Characteristics at Study Entry

	No. of Patients	%
Total	50	
Sex		
Male	22	44
Female	28	56
Age, years		
Mean	58.3	
Range	30-78	
Karnofsky performance score		
Mean	87.2	
Median	90	
Range	50-100	
Type of tumor		
Carcinoid	26	52
NE tumor unknown origin	7	14
NE tumor pancreas	13	26
Gastrinoma	3	6
Insulinoma	1	2
Metastases		
Liver	45	90
Bone	10	20
Prior therapy		
Surgery	22	44
Chemotherapy	5	10
Somatostatin analogs	24	48

Abbreviation: NE, neuroendocrine.

Eight patients were excluded from the analysis because of missing forms. Two of these had tumor regression, three had SD, two had PD, and in one patient no treatment outcome could be established. These treatment outcomes were not significantly different from the whole patient group (Fisher's exact test [two-sided]; $P > .05$). The total amount of missing items of all the EORTC QLQ-C30 questionnaires was 14 of 3,000, yielding a completion rate of 99.5%. These missing items were randomly distributed and therefore, simple mean imputation was considered appropriate to handle the data without the introduction of significant bias.[14]

The mean interval between baseline and first follow-up visit (6 weeks after the last therapy) was approximately 7 months (range, 5 to 12 months). This interval varied because in some patients, treatments had to be postponed as a result of sustained bone marrow suppresion, and because the number of treatments varied due to patients reaching their cumulative maximum kidney radiation dose. The latter was calculated for each indiviual patient separately, and varied considerably. All patients received between 600 and 800 mCi of ^{177}Lu-octreotate.

The EORTC QLQ-C30 data indicated that patients assigned high scores to the functional scales at baseline (Table 2). The role and cognitive function scales were given respectively the lowest (67.0) and the highest (88.7) scores. The score for the global health status/QoL scale (69.0) was slightly lower than most of the functional scales. The highest scores of the symptoms scales and single items were assigned to fatigue (31.9), insomnia (26.0), and pain (23.3), as well as diarrhea (16.7) and dyspnea (16.3).

The global health/QoL scale score changed significantly from 69.0 to 78.2 ($P < .01$). Moreover, significant improvements were demonstrated in the emotional function scale (77.7 to 85.8; $P < .001$), the role function scale (67.0 to 82.0; $P < .01$) and in the social function scale (80.7 to 90.3; $P < .01$). In the symptoms scale scores, fatigue and pain decreased from 31.9 to 22.8 ($P < .01$) and 23.3 to 15.0 ($P < .05$), respectively. Only insomnia, as one of the six single items, decreased 11.7 points in score ($P < .01$). At baseline, 17 (34%) of 50 patients had diarrhea as part of a secretory syndrome, versus 16 (32%) of 50 at the first follow-up visit ($P > .05$). However, patients who initially had diarrhea had a significant decrease in diarrhea score from 49.0 to 15.7 ($P < .0001$) after therapy. Only one patient in this group switched to morphine, which probably accounted for the observed decrease of diarrhea in this patient. Mean body weight increase during the average period of 7 months changed significantly from 71.3 to 74.0 kg ($P = .01$).

In the group with tumor regression, the global health/QoL scale score increased significantly from 70.1 to 80.6 ($P < .05$). The physical, role, emotional, and social scale improved with an increase in score of 6.0, 22.2, 10.0, and 11.1, respectively ($P < .05$). The score of the symptom scale fatigue decreased from 30.3 to 19.2 ($P < .01$) and the single item insomnia decreased from 23.6 to 8.7 ($P < .01$) after therapy. Body weight increased significantly from 72.4 to 77.2 kg ($P < .01$). The KPS did not change significantly (Fig 1).

In the group with stable disease, no significant changes were found in the functional scales. In patients with pain at baseline (13 of 19 patients; 68%), a significant decrease in score was found from 41.0 (baseline) to 17.9 (6 weeks after therapy; $P < .01$). In patients with stable disease ($n = 19$), no further significant change of any other score was found. In patients with progressive disease ($n = 6$), only the global health/QoL score increased from 48.6 to 72.2 ($P < .01$; Fig 2).

The change in score of the self-reported global health/QoL scale between before and after therapy was positively correlated with the change in KPS (Pearson's rank correlation; $\rho = 0.39$; $P < .01$). Twenty (60%) out of 33 patients who had a lower or equal KPS after therapy reported an increase in global health/QoL scale, and 12 (80%) of 15 patients who had a higher KPS after the therapy also had a higher global health/QoL scale score compared to baseline (Fig 3).

DISCUSSION

Treatment with radiolabeled somatostatin analogs, like ^{177}Lu-octreotate, in patients with metastasized neuroendo-

Table 2. Patients (n = 50) Mean Scores on EORTC QLQ-C30 Scales and Single Items

	At Baseline		Follow-Up (6 weeks)			
	Mean	SD	Mean	SD	Change	P^*
Global quality of life†						
Global health-status/quality of life	69.0	20.8	78.2	16.9	9.2	< .01
Functional scales†						
Physical	80.8	19.3	84.6	20.4	3.8	.07
Role	67.0	31.7	82.0	25.2	15.0	< .01
Emotional	77.7	15.7	85.8	15.5	8.1	< .001
Cognitive	88.7	16.0	88.3	17.3	−0.4	.89
Social	80.7	22.7	90.3	21.3	9.6	< .01
Symptom scales‡						
Fatigue	31.9	24.4	22.8	22.5	−9.1	< .01
Nausea/vomiting	6.7	16.5	5.0	11.3	−1.7	.46
Pain	23.3	28.8	15.0	20.0	−8.3	< .05
Single items‡						
Dyspnea	16.3	23.7	17.3	27.1	1.0	.71
Insomnia	26.0	30.3	14.3	21.5	−11.7	< .01
Appetite loss	10.2	19.5	8.7	21.1	−1.5	.70
Constipation	8.8	20.2	6.1	16.2	−2.7	.32
Diarrhea	16.7	26.3	12.2	18.9	−4.5	.26
Economical impact	5.3	14.1	5.3	15.6	0.0	.99
Body weight	71.3	14.5	74.0	15.5	2.7	.01
Karnofsky performance status scale	87.2	12.3	87.9	12.0	0.7	.52

NOTE. Mean scores and ± SD of the EORTC QLQ-C30 questionnaire before and after (6 weeks follow-up visit)^{177} Lutetium-octreotate therapy. Body weight and Karnofsky performance status are also shown.
Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; SD, standard deviation.
*$P < .05$ was regarded as statistically significant.
†Scores range from 0 to 100, with a higher score representing a higher level of function.
‡Scores range from 0 to 100, with a higher score representing a higher level of symptoms.

crine GEP tumors may be very rewarding in terms of tumor volume reduction.[7-9] Here, we report the outcome of health related quality-of-life (HRQoL) assessment before and after treatment with ^{177}Lu-octreotate. The EORTC QLQ-C30 scores of patients with metastasized GEP tumors at baseline indicated that the patients maintain a relatively good HRQoL. This is in line with a previous study by Larsson et al[15] in which the questionnaire was used to study the general HRQoL in patients with GEP tumors. Assessment of HRQoL data results in detailed information about many aspects of the patients' QoL, including symptoms, specific functional scales, and the overall health/QoL scale. The combined global health/QoL scale is regarded as the most important scale to score, as it gives an overall impression of the experienced HRQoL. Furthermore, it has been shown to be a good predictor of survival.[16,17]

To identify aspects of HRQOL in which the patients clearly had gained meaningful improvement, a significant change of more than five points was considered to be clinically important, according to the method described by Osoba et al.[13] The patients in our study experienced such an improvement of their global health/QoL after therapy with ^{177}Lu-octreotate. In addition, the role, emotional, and social function scale score showed a clinically important improvement. The symptom scales fatigue and pain and the single item insomnia were the only scores that were high at baseline and decreased significantly. Fatigue is the most frequently reported symptom in cancer patients, and its reason is often obscure.[18-20] Also, insomnia is reported in 30% to 50% of patients with cancer.[21] Profound diarrhea is a common symptom in patients with GEP tumors. However, we found no significant change in diarrhea, most probably because most patients with severe diarrhea used somatostatin analogs that resulted in an adequate symptom control. However, patients who still suffered from diarrhea before the start of ^{177}Lu-octreotate therapy did notice an improvement of this symptom.

The change in self-reported global health/QoL was positively correlated with the change in KPS as judged by the physician. Correlation between KPS scores and the different domains of QoL have been reported in other studies.[22,23] In these studies, however, it was concluded that, although associated, both measures are not assessing the same construct. Schaafsma et al[22] stated that the EORTC QLQ-C30 is a more comprehensive measure of QoL than the KPS. This is in line with the greater number of positive changes we found in the global health/QoL scale as reported by the patient, as compared with the changes in the physician-based KPS. Larsson et al[24] stated that patients with GEP tumors rated the physical aspects of life as the

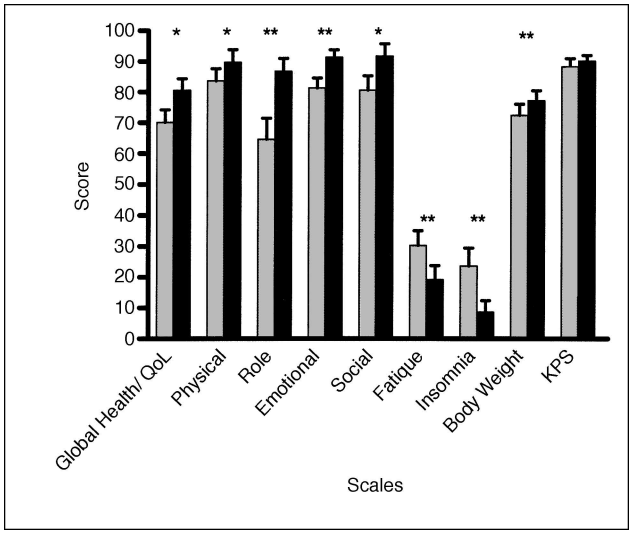

Fig 1. Changes in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 scales and Karnofsky performance score (KPS) in patients with tumor regression before (baseline) and at 6 weeks follow-up. Only scales that changed significantly are shown. SE to the mean are shown above each bar. Gray bars: before [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate therapy; black bars: after therapy. $*P < .05$; $**P < .01$.

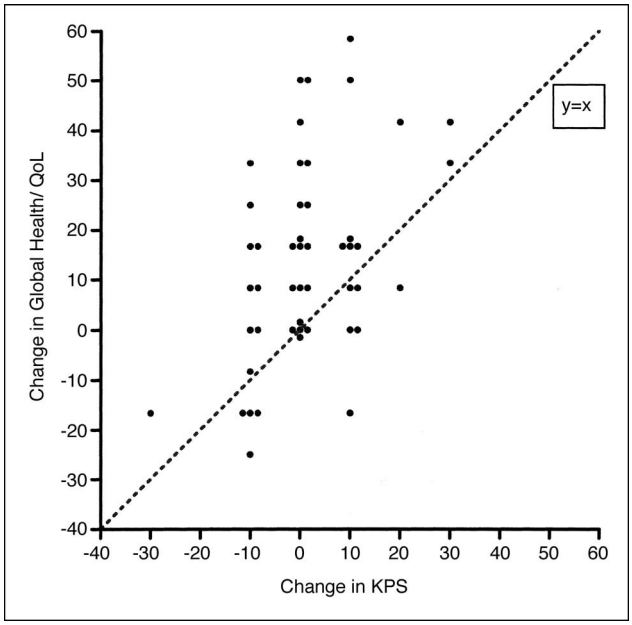

Fig 3. Changes in global health/quality of life (QoL) scores per patient versus changes in Karnofsky performance score (KPS). Values are scores at 6 weeks follow-up minus scores at baseline. The line (y = x) represents equal changes. Note that positive changes in global health/QoL scale are more frequent than positive changes in KPS.

most important aspect for experiencing a good HRQoL. In contrast, we found no evidence of significant change in the physical function scale, whereas other scales, including the global health/QoL, did increase significantly. Thus, although reported as the most important aspect of QoL, it appears that, when the level of physical functioning is relatively high as in our patients, aspects of QoL other than physical functioning become important to determine the patients' overall QoL.

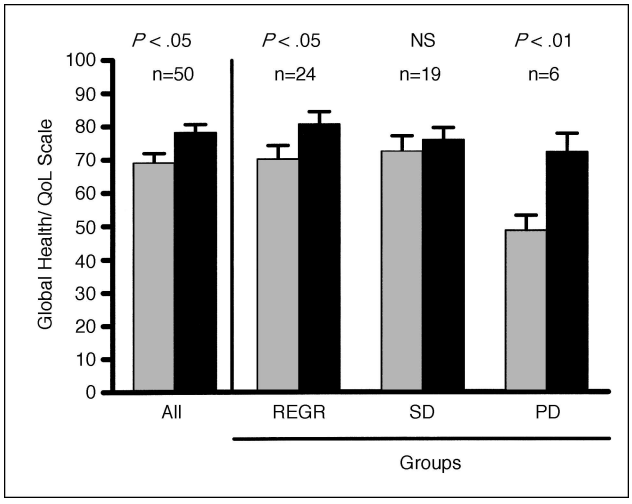

Fig 2. Global health/quality of life (QoL) scale scores of all the patients (N = 50) and the different outcome groups according to tumor evaluation before (gray bars) and after (black bars) [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate therapy. SE to the mean are shown above each bar. REGR, regression; SD, stable disease; PD, progressive disease; NS, not significant.

In the group with SD, no worsening of symptoms or decrease in functioning scales was found. However, considering the five (26%) of 19 patients who had documented PD in the year before therapy, a stabilization of any aspect of QoL suggests a positive effect of ^{177}Lu-octreotate therapy. Furthermore, patients with pain at baseline had a significant decrease in score with more than 20 points. Waldherr et al[25] reported similar findings of clinical benefit in a group of 21 patients with NE tumors treated with the radiolabeled somatostatin analog ^{90}Y-DOTATOC. However, they used a physician-based method, whereas we preferred to use a more patient-based method with the EORTC QLQ-C30. In contrast to the group of patients with SD, a significant improvement of the global health/QoL scale was found in patients with PD. The difference between the low score at baseline in the latter group, compared with the relatively high score in patients with SD, could explain this contradicting observation. In combination with the absence of any significant change in any other scale, it suggests that, in patients with PD, even a small change in any other scale could have had a large impact on their overall health/QoL. Because our group with PD represented a small number of patients and, moreover, one patient was lost to follow-up, the accuracy of these observations remains questionable. Also, a placebo effect cannot be ruled out completely.

In conclusion, we found that ^{177}Lu-octreotate therapy improved the QoL in patients with metastasized GEP tumors, especially in the patients with proven regression.

Beside this positive effect on the general well-being, specific functional scales and symptoms improved. These findings are clearly different from other traditional end points, like the effect of therapy on tumor volume and KPS, and therefore gives additional important insight in the effect of the therapy on the normal daily life of our patients.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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