Health-related Quality of Life, Anxiety and Depression in Patients with Midgut Carcinoid Tumours

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In earlier studies it has been reported that patients with carcinoid tumours have a relatively good health-related quality of life (HRQoL) and low levels of anxiety and depression. The aims of this study were (a) to investigate the extent to which psychosocial function changes in patients with carcinoid tumours with time from diagnosis and its possible relation to tumour markers, and (b) to compare the HRQoL of patients with carcinoid tumours with that of healthy Swedish adults. Twenty-four patients reported on HRQoL (the EORTC QLQ-C30), anxiety and depression (the Hospital Anxiety and Depression Scale) five times during their first year of treatment. After one year, improvement in nausea/vomiting, flush and anxiety was reported, but there was deterioration of physical function, an increase in muscular pain and problems with dry skin. Levels of tumour markers were not associated with psychosocial function. Patients reported a lower HRQoL compared with healthy Swedish adults. Thus, deterioration of physical function was not accompanied by a deterioration of emotional function, and levels of tumour markers were not related to patients' HRQoL.

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Carcinoid tumours belong to the family of neuroendocrine tumours which originate from the neuroendocrine cell system. The incidence of carcinoid tumours is around 0.5/100 000 (1). These tumours present features that are distinct from other malignant tumours. First, in most patients, tumour growth is fairly slow. Secondly, the tumours produce hormones that influence the clinical condition of the patient (2), the most common symptoms being flush, diarrhoea, bronchial constriction and right heart failure (the carcinoid syndrome) (3). Based on the site of origin, carcinoid tumours have been divided into foregut (bronchus, stomach, proximal duodenum and pancreas), midgut (distal duodenum to midtransverse colon) and hindgut (descending colon and rectum) (4), and the most common type is midgut carcinoid (5).

Treatment of carcinoid tumours is aimed to reduce hormone levels, control hormonal symptoms, prevent further tumour growth and also possibly to achieve tumour reduction. Whenever possible, systematic removal of all resectable tumours has been recommended (6, 7). Because the majority of patients present with a metastatic disease at the time of diagnosis, surgical treatment is not curative and medical treatment is warranted (8). Since the early 1980s, biotherapies such as α-interferon (α-INF) and somatostatin analogues have been introduced. These treatments have significantly improved the clinical management of carcinoid tumours (9), and they constitute the first-line medical treatment for patients with midgut carcinoid tumours.

Treatment of carcinoid tumours is seldom curative. However, improved diagnostic and therapeutic methods have prolonged life for many patients. The assumption that adding time, adds value, may often, but not always be correct. Few studies have evaluated health-related quality of life (HRQoL) in patients with carcinoid tumours. Jacobsen & Hanssen investigated HRQoL (10) in 11 patients with endocrine GI tumours, including those with carcinoid tumours, during treatment with a somatostatin analogue. The results demonstrated that two domains of HRQoL changed significantly during one month of therapy: ability to relate socially increased and psychosocial distress decreased. In another study (11), prolonged release of a long-acting somatostatin analogue was investigated in conjunction with HRQoL in patients with endocrine GI tu-

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Table 1

Characteristics of 24 patients with carcinoid tumour at the time of inclusion

Background variable	
Median time since diagnosis	3 months (range 1–96)
Resection of primary tumour	17 (71%)
Carcinoid syndrome	20 (83%)
Metastatic	18 (75%)
Level of chromogranin A ≥ 4 μg/L	23 (96%)
Level of U-5HIAA ≥ 80 μmol/24 h	15 (62%)
Treatment	
Interferon	15
Somatostatin analogue	1
Interferon and a somatostatin analogue	8
Median age	62 years (range 25–81)
Male/Female	14/10
Married-cohabiting	20
Children	22
Employed	10
Old-age pensioner	14

mours. HRQoL was assessed for a period of six months. After one month of therapy, emotional and cognitive functions as well as global health status improved significantly, while problems with fatigue, diarrhoea and sleeping problems were significantly reduced, as assessed by the EORTC QLQ-C30. Only diarrhoea continued to be significantly improved throughout the study. We have demonstrated (12–14) that patients with endocrine GI tumours report a relatively good HRQoL as well as low levels of anxiety and depression. The results suggest that patients enjoy a better HRQoL five years or more after diagnosis than they do closer to the diagnosis (14). Earlier HRQoL studies of this patient group (12–14) employed a cross-sectional design and so potential changes over time with regard to psychosocial function remains to be investigated. In addition, the extent to which psychosocial function is related to biochemical tumour markers remains to be clarified.

As mentioned above, the HRQoL of this patient group has been reported to be relatively good (12–14). However, no studies have been undertaken which make a comparison with a normative sample of the general population.

Taken together, patients with carcinoid tumours present specific symptoms of disease and side effects of treatment. Little is known about how these patients perceive their HRQoL. The aim of the present study was to investigate HRQoL, anxiety and depression in patients with midgut carcinoid tumours during one year of treatment. The following research questions were posed: (i) Do patients' ratings of HRQoL, anxiety and depression change during one year of treatment? (ii)) How do patients rate their HRQoL compared with a sample of the Swedish general population, before treatment and at 12 months after start of treatment? and (iii) Are there any correlations between patients' ratings of HRQoL, anxiety and depression on the one hand, and biochemical tumour markers at those points in time on the other?

MATERIAL AND METHODS

Twenty-four consecutive patients referred for medical treatment to the Department of Internal Medicine, Endocrine Oncology Unit, University Hospital, Uppsala were included in the study. Inclusion criteria were: patients should (a) have a histopathologically verified midgut carcinoid tumour, (b) be informed about their diagnosis, and (c) be scheduled for treatment with α-INF and/or a somatostatin analogue. During the study period, 34 patients were eligible. Ten patients were excluded because they (a) had been treated with chemotherapy and/or a biological response modifier during the preceding 12 months (n = 6), (b) had additional chemotherapy (n = 1), or (c) did not speak or read Swedish (n = 3). Patient (n = 24) characteristics at the time of inclusion are presented in Table 1. Six patients did not complete the study, owing to death (n = 3) or treatment termination (progressive disease n = 2, toxicity n = 1). Reasons for missing data at each assessment point are presented in Table 2.

Instruments

Before start of treatment (baseline), patients were asked to specify age, gender, marital status, whether they had children, occupational status, time of diagnosis and type of treatment.

Functional ability was assessed by the Karnofsky Performance Status Scale (KPS) (15), rated by a physician at

Table 2

Reasons for missing data and number of participants at the 3, 6, 9 and 12-month follow-ups

Reason for missing data	3 months n	6 months n	9 months n	12 months n
Administrative failure	–	3	3	–
Death	1	2	2	3
Progressive disease	–	1	2	2
Unrelated surgery	2	–	–	–
Toxicity	–	1	1	1
Participants	21	17	16	18

baseline and at 3, 6, 9 and 12 months after treatment start. The KPS is an 11-point numerical scale, ranging from normal functioning (= 100) to death (= 0) and has been found to have sufficient reliability and validity for assessing functional ability (16).

The EORTC QLQ-C30 (version 2.0) (17) was used to assess patient HRQoL at baseline and at 3, 6, 9 and 12 months after treatment start. The EORTC QLQ-C30 includes 30 items and is composed of five functional scales (physical, role, cognitive, emotional, social), and three symptom scales (fatigue, pain, nausea/vomiting), one global health status/QoL scale, and six single items (dyspnoea, appetite loss, insomnia, constipation, diarrhoea, financial problems). In accordance with the scoring instructions given by the EORTC Quality-of-Life Study Group (17), the scores are linearly transformed to 0–100 scores. For the functional, global health and overall QoL scales, a higher score means a higher level of functioning. For the symptom-oriented scales and single items, a higher score corresponds to a higher level of symptoms. The EORTC QLQ-C30 has been found to have adequate reliability and validity for assessing HRQoL (17).

Separate questions not covered by the EORTC QLQ-C30 were used to assess the occurrence and intensity of the most common disease- and treatment-related symptoms, according to our clinical experience. Patients were asked to report on whether they had experienced flush, muscular pain, fever or dry skin at baseline and at 3, 6, 9 and 12 months after start of treatment. Each item has four response alternatives with scores ranging from 1, indicating no problem, to 4, indicating a high level of problems. The questions were developed and used in previous studies (12, 13) of patients with endocrine GI tumours.

Anxiety and depression were assessed at baseline and at 3, 6, 9 and 12 months after treatment start by means of the Hospital Anxiety and Depression Scale (HADS), which is a self-assessment scale consisting of two subscales, one measuring anxiety (7 items) and the other depression (7 items). Each item has four possible answers, with scores from 0, indicating no problem, to 3 indicating a high level of problems. The HADS is found to have sufficient reliability and validity for detecting anxiety and depression in somatically ill patients (18).

Plasma levels of chromogranin-A (reference range < 4 μg/L) and the urine serotonin metabolite 5-hydroxyindoleacetic acid (U-5-HIAA) (reference range < 80 μmol/24 h) were used as biochemical tumour markers and were assessed at baseline and at 3, 6, 9 and 12 months after treatment start.

Procedure

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Uppsala University, and informed consent was obtained from all subjects. Patients completed the questionnaires, and plasma chromogranin A and U-5HIAA were determined at the Endocrine Oncology Unit. The patients were instructed on how to complete the questionnaires by the first author, who was present on all assessment occasions.

Data analysis

One-sample t-tests were employed to investigate whether the mean ratings of HRQoL, anxiety and depression, and levels of tumour markers at 3, 6, 9 and 12 months differed significantly from those at baseline. Pearson's product moment correlations were computed between, on the one hand, HRQoL, anxiety and depression scores and, on the other, scores for the biochemical tumour markers.

In order to make valid comparisons of patient ratings of the EORTC QLQ-C30 with normative data from the Swedish population (19), corrections were made for age and gender differences (20). This procedure also corrects for differences in comorbidity between patient samples and normative samples. Expected scores were computed, using the Swedish population reference score for each age and gender group (20). A difference of more than 10 points between the observed and expected values was considered as clinically significant (21, 22). One-sample t-tests were employed to analyse whether the observed scores differed significantly from the expected ones.

RESULTS

HRQoL, anxiety and depression

The KPS baseline mean was 90 (SD = 7.2), and there were no significant differences between that score and any of the remaining assessments.

Table 3 presents mean scores and standard deviations for the EORTC QLQ-C30 ratings at baseline, 3, 6, 9 and 12 months, and mean difference scores between baseline and each of the other assessment points. Significant differences were found for two scales. The mean scores for physical function were lower at 6 months ($p < 0.01$), 9 months ($p < 0.05$) and 12 months ($p < 0.01$) compared with the baseline scores. Similarly, the score for nausea/vomiting was lower at 12 months ($p < 0.05$) compared with baseline.

Table 4 presents data for the ratings of the disease- and treatment-related questions. The scores for flush were significantly lower at 9 months ($p < 0.05$) and 12 months ($p < 0.05$) compared with those at baseline, as was the rating for fever at 3 months ($p < 0.05$). The rating for muscular pain was significantly higher at 12 months ($p < 0.01$), as was the rating for dry skin ($p < 0.05$), compared with the baseline values.

Table 4 also presents data for the HADS subscales. The anxiety rating was lower at 12 months ($p < 0.05$), and the score for depression was significantly higher at 9 months ($p < 0.01$) than the baseline values.

Table 3

Patient mean scores (SD) for EORTC QLQ-C30 scales and single items, and mean difference scores (D) relative to baseline

Scale	Baseline (n = 24)		3 months (n = 21)			6 months (n = 17)			9 months (n = 16)			12 months (n = 18)		
	M	(SD)	M	(SD)	D	M	(SD)	D	M	(SD)	D	M	(SD)	D
Physical function [a]	85	(20)	80	(23)	−6	71	(31)	−21**	71	(31)	−18*	70	(22)	−20**
Role function [a]	65	(33)	76	(32)	+9	67	(36)	−9	67	(32)	+1	76	(25)	+7
Emotional function [a]	73	(21)	75	(28)	+1	79	(16)	+1	79	(14)	−1	80	(15)	+8
Cognitive function [a]	83	(20)	81	(23)	−2	83	(14)	−7	84	(13)	+1	87	(14)	+7
Social function [a]	85	(20)	83	(24)	−4	82	(20)	−2	74	(29)	−8	78	(24)	−6
Global health/quality of life [a]	68	(23)	59	(28)	−11	58	(23)	−7	57	(19)	−12	63	(13)	−3
Fatigue [b]	36	(24)	35	(31)	+1	39	(32)	+6	40	(30)	+4	38	(20)	+7
Nausea/vomiting [b]	19	(24)	16	(27)	−3	8	(12)	−6	5	(10)	−10	4	(7)	−9*
Pain [b]	19	(24)	23	(29)	+4	23	(30)	+9	24	(33)	+8	25	(17)	+12
Dyspnoea [b]	19	(28)	16	(27)	0	25	(36)	+12	23	(32)	+6	20	(26)	+4
Insomnia [b]	24	(35)	21	(31)	+2	22	(33)	−2	25	(35)	0	24	(25)	+4
Appetite loss [b]	25	(34)	32	(41)	+11	25	(32)	+2	19	(30)	−6	20	(35)	−4
Constipation [b]	15	(29)	5	(12)	−13	10	(20)	−2	4	(11)	−8	4	(11)	−9
Diarrhoea [b]	46	(39)	32	(37)	−10	37	(33)	−12	38	(38)	−15	43	(38)	−7
Financial difficulties [b]	6	(16)	3	(10)	−2	10	(19)	+4	13	(21)	+6	7	(24)	+2

[a] Scores range from 0 to 100, a higher score representing a higher level of function.
[b] Scores range from 0 to 100, a higher score representing a higher level of symptoms.
*p < 0.05; **p < 0.01.

In order to compare these results with the normative data, corrections for age and gender were made for the EORTC QLQ-C30 data. Table 5 presents observed and expected scores at baseline and at 12 months. At baseline, the observed score was more than 10 points or more below the expected one for two functional scales (role function − 20, emotional function − 12), and more than 10 points or more above for four symptom scales/items (fatigue + 15, nausea/vomiting + 16, appetite loss + 21, diarrhoea + 40). At 12 months, the mean score was more than 10 points below the expected score for three functional scales (physical − 17, social − 13, global health/quality of life − 13), and more than 10 points above for three symptom scales/items (fatigue + 18, appetite loss + 16, diarrhoea + 38). All these differences, with the exception of that for appetite loss at 12 months, were statistically significant according to one-sample t-tests ($p < 0.05$).

In summary, there were few significant changes in the ratings of HRQoL, anxiety and depression during the study period. Patients reported a lower HRQoL compared to that of the Swedish general population, both at baseline and at the 12-month assessment.

Table 4

Patient mean scores (SD) for disease- and treatment-related questions and the HADS subscales, and mean difference scores (D) relative to baseline

Item/Scale	Baseline (n = 24)		3 months (n = 21)			6 months (n = 17)			9 months (n = 16)			12 months (n = 18)		
	M	(SD)	M	(SD)	D	M	(SD)	D	M	(SD)	D	M	(SD)	D
Flush [a]	1.9	(0.9)	1.8	(0.7)	−0.1	1.7	(0.7)	−0.3	1.6	(0.7)	−0.6*	1.4	(0.6)	−0.6*
Muscular pain [a]	1.3	(0.6)	1.6	(0.9)	+0.2	1.6	(1.0)	+0.3	1.9	(1.1)	+0.6	1.8	(0.7)	+0.5**
Fever [a]	1.4	(0.9)	1.2	(0.5)	−0.3*	1.1	(0.3)	−0.3	1.1	(0.5)	−0.3	1.2	(0.5)	−0.3
Dry skin [a]	1.6	(0.8)	1.6	(0.8)	+0.1	1.8	(1.1)	+0.4	1.8	(0.8)	+0.2	2.2	(1.1)	+0.6*
Anxiety [b]	4.6	(4.0)	4.4	(4.5)	0	4.5	(3.8)	+0.2	4.2	(2.2)	−0.2	3.0	(2.4)	−1.9*
Depression [b]	3.2	(2.7)	3.5	(3.4)	+0.5	4.8	(4.0)	+1.7	5.2	(3.7)	+1.8**	3.7	(2.2)	+0.6

[a] Scores range from 1 to 4, a higher score representing a higher level of problems.
[b] Scores ranging from 0 to 21, a higher score representing a higher level of problems.
*p < 0.05; **p < 0.01.

Table 5

Expected (population-based) and observed mean scores for the EORTC QLQ-C30 scales and single items, at baseline (n = 24) and at 12 months (n = 18)

EORTC QLQ-C30 scales/single items	Baseline			12 months		
	Observed score	Expected score	Obs.–Exp. difference	Observed score	Expected score	Obs.–Exp. difference
Physical function [a]	85	85	0	70	87	−17**
Role function [a]	65	85	−20**	76	86	−10
Emotional function [a]	73	85	−12*	80	84	−4
Cognitive function [a]	83	88	−5	87	88	−1
Social function [a]	85	91	−6	78	91	−13*
Global health/ quality of life [a]	68	76	−8	63	76	−13**
Fatigue [b]	36	21	+15**	38	20	+18**
Nausea/vomiting [b]	19	3	+16**	4	3	+1
Pain [b]	19	20	−1	25	20	+5
Dyspnoea [b]	19	19	0	20	19	+1
Insomnia [b]	24	19	+5	24	21	+3
Appetite loss [b]	25	4	+21**	20	4	+16
Constipation [b]	15	6	+9	4	5	−1
Diarrhoea [b]	46	6	+40***	43	5	+38***
Financial difficulties [b]	6	6	0	7	7	0

[a] Scores range from 0 to 100, a higher score representing a higher level of function.
[b] Scores range from 0 to 100, a higher score representing a higher level of symptoms.
*p < 0.05; ** < 0.01; ***p < 0.001.

Table 6

Mean values (SD) for biochemical tumour markers (plasma chromogranin A and U-5HIAA), and differences (D) relative to baseline

	Baseline (n = 24)		3 months (n = 21)			6 months (n = 17)			9 months (n = 16)			12 months (n = 18)		
	M	(SD)	M	(SD)	D	M	(SD)	D	M	(SD)	D	M	(SD)	D
Chromogranin A [a]	104	(198)	77	(159)	−29*	91	(153)	−14	97	(155)	−8	83	(130)	−12
U-5HIAA [b]	337	(551)	221	(466)	−68**	319	(530)	−140**	288	(442)	−180*	212	(340)	−126

[a] reference range <4 μg/l.
[b] reference range < 80 μmol/24 h.
* p < 0.05.
** p < 0.01.

HRQoL, anxiety and depression in relation to biochemical tumour markers

Table 6 presents the levels of plasma chromogranin A and U-5HIAA. U-5HIAA was significantly lower at 3 months ($p < 0.05$), 6 months ($p < 0.01$) and 9 months ($p < 0.05$) compared with the baseline values. Chromogranin A was significantly lower at 3 months ($p < 0.05$) compared with the baseline values. The following significant correlations were found: the rating of diarrhoea at 12 months was positively associated with levels of plasma chromogranin A ($r = 0.48$, $p < 0.05$) and with U-5HIAA ($r = 0.68$, $p < 0.01$). The rating of depression at 12 months was associated with plasma chromogranin A ($r = 0.51$, $p < 0.05$). In view of the low number of patients, scatterplots were examined for potential outliers, but, none was identified.

DISCUSSION

HRQoL, anxiety and depression were monitored in patients with midgut carcinoid tumours during one year of treatment with α-INF and/or a somatostatin analogue. The reported HRQoL, anxiety and depression scores agree with those reported earlier in patients with endocrine GI tumours (13, 14). The ratings did not change substantially during the study period, and observed changes were both for the worse (physical function, muscular pain, dry skin, depression) and for the better (nausea/vomiting, flush, fever, anxiety).

Depression is a known side effect of α-INF (2). However, reported levels of depression (HADS) were relatively low. According to the medical records, only a few patients suffered from depression, and those who developed symptoms of depression were successfully treated with antidepressants.

It is of clinical interest to investigate the possible differences between those treated with α-INF only (n = 9) and those treated with both a-INF and a somatostatin analogue (n = 8). At 12 months, there were significant differences for two EORTC QLQ-C30 scales and for the HADS anxiety subscale. The patients treated with both agents rated their overall HRQoL (QL) higher (m = 72), and problems with sleep (SL) lower (m = 13) than those treated with a-INF alone [QL: (m = 56, $p < 0.05$), SL: (m = 37, $p < 0.05$)]. The group treated with both agents also rated their anxiety lower (m = 1.5) compared to the group treated with α-INF only (m = 4.3) ($p < 0.05$). Although the number of patients is very small, these findings suggest that the group treated with both agents had fewer problems than the group treated with α-INF only.

It is interesting to note that those aspects of HRQoL that deteriorated significantly from baseline to the 12-month follow-up were of a physical character, while emotional aspects did not deteriorate, and the level of anxiety even improved significantly. At baseline, the reported emotional function was significantly worse than that expected for people of similar age and gender. However, at 12 months, this difference was no longer significant. Thus, the patients appear to have been successful in coping with the emotional demands of their disease and treatment, despite the aggravation of the physical symptoms of disease and treatment. Little is known about how patients with carcinoid tumours deal with the demanding situation caused by the disease and its treatment at various points in time after diagnosis. Even less is known about how these patients cope with the specific aspects of disease and treatment.

Earlier studies (12–14), indicate that patients with endocrine GI tumours enjoy a relatively good HRQoL. However, in these studies the comparison was made with other patients groups. Such comparisons are not readily interpreted, because of differences in symptomatology, treatment and time of survival. The present comparison of patient scores on the EORTC QLQ-C30 with expected scores for the Swedish general population (19) yield an estimate of the HRQoL of patients with carcinoid compared to healthy people. The comparison revealed that the patients had a lower HRQoL than expected for healthy people of similar age and gender, both at baseline and at 12 months.

Few correlations were demonstrated between tumour markers and ratings of HRQoL, anxiety and depression. Significant correlations were identified between plasma chromogranin A and U-5HIAA, and diarrhoea at 12 months. This result was expected, since serotonin is involved in the mechanism regulating diarrhoea (23). Ratings of depression at 12 months were significantly associated with the level of plasma chromogranin A. There is no ready explanation for this observation.

Carcinoid tumours are rare, and patient samples in available studies are usually small. In addition, there is the problem of missing data. These circumstances may have contributed to the lack of statistically significant results in the present study. However, another possible explanation for the relative lack of significant results might be that the EORTC QLQ-C30 as well as the HADS lack content validity for measuring the psychosocial function of patients with carcinoid tumours. It is known that HRQoL is related to the attainment of important aspects of life (24). None of the questionnaires used in the present study have been developed for use with this group of patients and may therefore lack some important aspects. A reliable and valid assessment tool is needed that will cover the major disease- and treatment-related problems of this specific group of patients.

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REFERENCES

1. Norheim I, Öberg K, Theodorsson-Norheim E, et al. Malignant carcinoid tumors. An analysis of 103 patients with regard to tumor localization, hormone production, and survival. Ann Surg 1987; 206: 115–25.
2. Öberg K. Endocrine tumors of the gastrointestinal tract: systemic treatment. Anticancer Drugs 1994; 5: 503–19.
3. Grahame-Smith DG. The carcinoid syndrome. Am J Cardiol 1968; 21: 376–87.
4. Williams ED, Sandler M. The classification of carcinoid tumours. Lancet 1963; 1: 238–9.
5. Modlin IM, Sandor A. An analysis of 8 305 cases of carcinoid tumors. Cancer 1997; 79: 813–29.
6. Loftus JP, van Heerden JA. Surgical management of gastrointestinal carcinoid tumors. Adv Surg 1995; 28: 317–36.
7. Norton JA. Surgical management of carcinoid tumors: role of debulking and surgery for patients with advanced disease. Digestion 1994; 55: 98–103.
8. Öberg K. Neuroendocrine gastrointestinal tumors—a condensed overview of diagnosis and treatment. Ann Oncol 1999; 10: S3–8.
9. Öberg K. Advances in chemotherapy and biotherapy of endocrine tumors. Curr Opin Oncol 1998; 10: 58–65.
10. Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours. Report on a double-blind, randomized trial. J Intern Med 1995; 237: 269–75.
11. Wymenga AN, Eriksson B, Salmela PI, et al. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. J Clin Oncol 1999; 17: 1111–7.
12. Larsson G, von Essen L, Sjödén PO. Quality of life in patients with endocrine tumors of the gastrointestinal tract: patient and staff perceptions. Cancer Nurs 1998; 21: 411–20.
13. Larsson G, von Essen L, Sjödén PO. Health-related quality of life in patients with endocrine tumours of the gastrointestinal tract. Acta Oncol 1999; 38: 481–90.

14. Larsson G, Sjödén PO, Öberg K, von Essen L. Importance-satisfaction discrepancies are associated with health-related quality of life in five-year survivors of endocrine gastrointestinal tumours. Ann Oncol 1999; 10: 1321–7.
15. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapuetic agents in cancer. In: McLeod CM, ed. Evaluation of chemotherapeutic agents in cancer. New York: Columbia University Press, 1949: 191–205.
16. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 1984; 53: 2002–7.
17. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365–76.
18. Moorey S, Greer S, Watson M, et al. The factor structure and factor stability of the Hospital Anxiety and Depression Scale in patients with cancer. Br J Psychiatry 1991; 158: 255–9.
19. Michelson H, Bolund C, Nilsson B, Brandberg Y. Health-related quality of life measured by the EORTC QLQ-C30-reference values from a large sample of the Swedish population. Acta Oncol 2000; 39: 477–84.
20. Hjermstad MJ, Fayers PM, Bjordal K, Kaasa S. Using reference data on quality of life-the importance of adjusting for age and gender, exemplified by the EORTC QLQ-C30 (+ 3). Eur J Cancer 1998; 34: 1381–9.
21. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res 1996; 5: 555–67.
22. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16: 139–44.
23. Feldman JM, O'Dorisio TM. Role of neuropeptides and serotonin in the diagnosis of carcinoid tumors. Am J Med 1986; 81: 41–8.
24. Montgomery H, Johansson US. Life values: their structure and relation to life situation. In: Maital IS, ed. Applied behavioral economics. Brighton: Whealsheaf, 1988: 420–37.