Quality of Life in Patients with Endocrine Gastrointestinal Tumours

BY

GUNNEL LARSSON
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ABSTRACT

The overall aim of this thesis is to investigate health-related quality of life (HRQoL), anxiety and depression in patients with endocrine gastrointestinal (GI) tumours. Patient as well as staff perceptions were assessed. HRQoL was studied with the EORTC QLQ-C30, and anxiety and depression with the Hospital Anxiety and Depression Scale. In addition, patient perceptions of the importance of and satisfaction with selected HRQoL aspects were investigated. Semi-structured interviews with open-ended questions were conducted to identify disease- and treatment-related distress, what constitutes a good quality of life and strategies to "keep a good mood" among these patients. Patients reported a relatively good HRQoL and low levels of anxiety and depression. However, they reported a lower HRQoL than could be expected for healthy people of similar age and gender. Staff gave a more pessimistic view of patient satisfaction with HRQoL aspects than did patients, and staff did not accurately judge individual patients' levels of anxiety and depression. Importance>satisfaction discrepancies for HRQoL aspects may identify patients with a low quality of life. HRQoL, anxiety and depression did not change substantially during the first year of treatment. Categories identified through content analysis of interview data concerning distress and quality of life were referred to physical, emotional or social dimensions. Identified strategies to "keep a good mood" were classified as Internal or External. Most categories of distress that were identified are covered by the EORTC QLQ-C30 and/or the HADS, but some additional emotional and social aspects of distress emerged from the interview data. Receiving good care was identified as a strategy to "keep a good mood". This result indicates a possible and potentially important relation between the quality of care and patient HRQoL.

Key words: Endocrine gastrointestinal tumours, health-related quality of life, psychosocial function, importance-satisfaction discrepancies.

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"The chief aim of science is not to open a door to infinite wisdom but to set limit to infinite error"

Bertolt Brecht
This doctoral thesis consists of the present summary and the following papers, which are referred to by their Roman numerals.


IV. Larsson, G, Sjödén, PO, Öberg, K, Eriksson, B and von Essen, L. Quality of life, anxiety and depression in patients with carcinoid tumours during the first year of treatment with α-interferon and/or a somatostatin analogue. Manuscript submitted for publication.


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RESULTS

Summaries of Studies I-V

Study I: Quality of life in patients with endocrine tumors of the gastrointestinal tract: patient and staff perceptions.

Study II: Health-related quality of life in patients with endocrine tumors of the gastrointestinal tract.

Study III: Importance-satisfaction discrepancies are associated with health-related quality of life in five-year survivors of endocrine gastrointestinal tumors.

Study IV: Quality of life, anxiety and depression in patients with carcinoid tumors during the first year of treatment with \( \alpha \)-interferon and/or a somatostatin analogue.

Study V: Distress, quality of life and strategies to "keep a good mood" in patients with carcinoid tumors: patient and staff perceptions.
INTRODUCTION

Carcinoid and endocrine pancreatic tumours (EPT) belong to the family of endocrine gastrointestinal (GI) tumours which derive from the neuroendocrine cell system [1]. These tumours are histologically similar and share a number of features. They are rare and constitute about 2% of all malignant GI tumours. In many patients, tumour growth is rather slow and a majority of the clinical symptoms are due to hormone release from the tumour [2].

Carcinoid tumours

The incidence of malignant carcinoid tumours is around 5 per million population [3]. However, the clinical presentation of carcinoid tumours far underestimates their occurrence, since many are asymptomatic. This is demonstrated by the fact that the annual incidence rate has been reported to be 2.8 per million population [4], whereas in autopsy studies an annual incidence of 21 per million [5].

The reported five-year survival rate for patients with carcinoid tumours varies [6]. Studies from the 1960s reported a rate of 21% for patients with carcinoid tumours [7], whereas those performed during the 1970s-90s have reported a rate of 50% to 80% [3, 8, 9]. A recent study has demonstrated a five-year survival rate of 63% [10] in a Swedish sample.

Carcinoid tumours can be ubiquitous, but most occur at bronchus, appendix, rectum and jejunooileum [9]. Based on the site of origin, carcinoid tumours have been divided into foregut (bronchus, stomach, proximal duodenum and pancreas), midgut (distal duodenum to mid-transverse colon) and hindgut (descending colon and rectum) tumours [11]. The most common tumour localisation is the GI tract (74%), and within the GI tract most tumours occur in the small bowel (29%), appendix (20%) and rectum (13%) [8].

The presentation of carcinoid tumours is diverse and related to the site of origin of the tumour as well as the malignant spread. In the appendix, the tumours are almost always found incidentally during surgery for a suspected appendicitis [12]. For the other tumour sites, abdominal pain due to the tumour itself, metastases or fibrosis of the mesentery (caused by
the tumour) may occur. The most common symptomatic feature is the carcinoid syndrome. This comprises flush, diarrhoea, right heart failure and bronchial constriction \[13\]. The syndrome occurs when hormonal products, released by the tumour, reach the systemic circulation. The occurrence and severity of the carcinoid syndrome is directly related to tumour size and whether the tumour site is in an area that drains into the systemic circulation [6].

The typical flush is the sudden appearance of a deep red or violet erythema of the upper part of the body, primarily the face and the neck. Flushing attacks may be brief, lasting 2 to 5 minutes or may be prolonged for hours. Flushing attacks occur in 63 [14] to 75% of patients [3]. Diarrhoea is typically described as watery stools with a frequency ranging from 2 to 30 per day and diarrhoea is present in 73 [14] to 84% [3] of the cases. Cardiac manifestation, involving primarily the right side of the heart is present in 14 [14] to 33% [3] of the patients. Bronchial constriction with wheezing or asthma-like symptoms occurs in 3 [14] to 15% [3] of the patients.

**Endocrine pancreatic tumours**

The incidence of EPT is around 4 per million population [15]. EPTs are considered as functional if they are associated with a clinical syndrome that is due to ectopic hormone release, and non-functional if not so associated.

The survival rate of patients with EPT varies depending on the syndrome. However, overall median survival for patients with malignant tumours has been reported to be 30 months [16]. Patients with functional tumours have a slightly shorter median survival (25 months) than patients with non-functional tumours (30 months). One study [17] has reported a median survival of 50 months (functional tumours 60 months, non-functional 50 months) for patients with malignant EPT.

The clinical characteristics of functional EPT depend on the specific hormone that is released by the tumour. The Zollinger-Ellison or gastrinoma syndrome which is due to gastrin
overproduction may lead to peptic ulcer disease or diarrhoea [18]. The hypoglycaemic syndrome or insulinoma which is due to insulin/proinsulin overproduction [19] may result in visual disturbances, confusion, an altered consciousness, sweating and pallor [20]. The Verner-Morrison syndrome [21] which is caused by high levels of vasoactive intestinal peptides may give rise to secretory diarrhoea with hypokalemia, dehydration and weight loss. The glucagonoma syndrome [22] is due to glucagon production and may give necrolytic migratory erythema, glucose intolerance, weight loss and anaemia. The somatostinoma syndrome [23, 24], due to somatostatin production may lead to diabetes mellitus, cholelithias, diarrhoea, steatorrhea and weight loss. In rare instances, EPT may produce hormones giving rise to Cushing's syndrome, acromegaly and an inappropriate antidiuretic hormone secretion [25-27].

**Diagnosis**

Carcinoid tumours and EPT are suspected when the classical clinical symptoms occur. The initial diagnosis is based primarily on biochemical tumour markers, that are selected according to the presenting clinical symptoms. Beside the hormones, chromogranin A [28] is the most important screening marker which is present in almost all neuroendocrine cells and is elevated in about 80-100% of patients with carcinoid tumours or EPT.

For localisation of endocrine GI tumours, the basic program includes computerised tomography scan, magnetic resonance imaging, ultrasound investigations, somatostatin receptor scintigraphy and positron emission tomography [29].

The final diagnosis should be based on histopathology, demonstrated by either a silver staining method (Grimelius staining) or immunohistochemistry for chromogranin A, synaptophysin or neuron-specific enolase [29].
Treatment

The aims of treatment are to reduce hormone levels, control hormonal symptoms, prevent further tumour growth and possibly also achieve tumour reduction, i.e. prolong survival and improve quality of life.

Whenever possible systematic surgical removal of all resectable tumour has been recommended for both carcinoid tumours and EPT [30-33]. Since the majority of patients present with a metastatic disease at the time of diagnosis, surgical treatment is not curative why medical treatment is warranted [29]. Medical treatment includes mainly chemotherapy, α-interferon (α-INF) and somatostatin analogues.

Chemotherapy constituted the basis for medical treatment of endocrine GI tumours during the 1970s and 1980s. Chemotherapy has been used in patients with carcinoid tumours or EPT as a single agent or in various combinations. The response rate in patients with carcinoid tumours has been reported to be low and short-lasting [6, 34, 35], whereas the response rate to chemotherapy in patients with EPT is better and has a longer duration [6, 36, 37].

During the 1980s, α-INF and somatostatin analogues were introduced and these treatments have significantly improved the clinical management of endocrine GI tumours [38]. α-INF is effective in controlling symptoms in patients with endocrine GI tumours [39-44]. It has an antitumoural effect in these tumours [40] and a significant impact on survival [2, 43, 45]. The optimal dose for long-time treatment seems to be 5 to 10 million units 3-5 times a week. However, it is important to titrate the dose individually for each patient [44]. α-INF is given as subcutaneous injections, mostly by the patient. α-INF has been associated with side effects including flu-like symptoms, chronic fatigue, weight loss, anaemia, depression, muscle pain, increased serum levels of triglycerides and increased liver enzymes [46]. Most of the adverse reactions are dose-related and can be handled by individual adjustment of doses.

Somatostatin analogues inhibit the release of various peptide hormones, and have proven to be effective in controlling the symptoms of carcinoid tumours and EPT [47-49]. Somatostatin
analogue available for clinical use are octreotide, lanreotide and RC-160, and the most
commonly used is octreotide. The optimal dose for controlling clinical symptoms is 100-150
µg administered 2-3 times a day [29]. Octreotide is given as subcutaneous injections, mostly
by the patient. Recently, long-acting depot formulas have been developed, which are given 1-
2 times per month. The response to octreotide varies markedly why it is important to titrate
the dose in each patient until adequate symptom and biochemical control is achieved [50].
Adverse effects of somatostatin analogues are rather limited [50], including nausea, abdominal
cramps, flatulence, diarrhoea and local reactions at the injection site, most of which resolve
with time. In some patients gallstones are formed de novo, and these mostly remain virtually
asymptomatic [51].

It has been shown that for carcinoid tumours, the combination of α-INF and octreotide
produces a stronger biochemical response than either drug alone [52, 53] and there are similar
indications for EPT [50].

Other treatment options are embolization of the hepatic artery with a variety of sclerosing
agents which may produce a biochemical and tumour response varying in duration [54-56].
Also, effects of metaiodobenzylguanidine have been reported [57]. Current research is directed
towards radiolabeled somatostatin analogues [58, 59].

**Quality of life in cancer patients**

During the first half of the past century, health was assessed mostly in terms of survival and
morbidity. When the World Health Organization (WHO) suggested that health is a state of
physical, mental and social well-being in addition to the absence of infirmity and disease [60],
this generated a broader concept of health, including physical, mental as well as social
dimensions. There is no consensus about how to define quality of life but it is considered to
be a broader concept than health. For example, Calman [61] suggests that quality of life is the
gap between the patients' expectations and achievements, and the smaller the gap, the higher
is quality of life. Kaplan and Bush [62] proposed the term health-related quality of life
(HRQoL) to distinguish the broad quality of life concept from those aspects of life quality that
are specifically relevant to health status and health care. Cella [63] suggested that the concept of HRQoL should be used to refer to the extent to which one's usual or expected physical, emotional and social well-being is affected by a medical condition or its treatment. Shumaker and Naughton [64] proposed a broader definition: "Health-related quality of life refers to people's subjective evaluations of the influence of their current health-status, health care and health promoting activities on their ability to achieve and maintain a level of overall functioning that allows them to pursue valued life goals and that is reflected in their general well-being. The domains of functioning that are critical to HRQoL include: social, physical and cognitive functioning, mobility and self-care, and emotional well-being" (p. 7).

Veenhoven [65] recently argued that the most inclusive measures of quality of life is how long and how happily people live.

**Why measure HRQoL and who should measure it?**

HRQoL has become an essential outcome measure in the evaluation of treatments for cancer patients. Knowledge about HRQoL may be of help in decision-making in clinical practice, may give important information about long-term effects in cancer survivors and help to identify potential adjustment problems. HRQoL evaluation differs from classical toxicity ratings in two important ways. Firstly, it incorporates more functional aspects (e.g. mood, affect, social well-being) than those which have typically been attributed to treatment, and secondly, it focuses on the patient's perspective [66]. It has been argued that measures of HRQoL should include those elements of HRQoL that (a) are sensitive to changes over time, (b) can be reliably and validly assessed, and (c) account for most of the variance in an individual's rating of his/her overall well-being [64].

Quality of life is dependent upon the interpretations and perceptions of the individual [67]. Thus, it can be assumed to mean different things to different individuals and different things to the same person in different phases of the disease trajectory. Research on HRQoL most often focuses on the extent to which patients experience the attainment of various "states" that are a priori regarded as desirable. However, it has been suggested that different individuals may assign different levels of desirability to the same states [68-72]. Cohen [73] has pointed out
that the simple listing of quality of life domains is not a satisfactory way of assessing quality of life because it is unknown whether all important domains have been included. An important objective of HRQoL assessment should therefore be to determine how a patient functions in those HRQoL areas that he/she judges to be most desirable and/or important, and how ratings of importance of and satisfaction with HRQoL aspects are related.

Various methods have recently been developed for assessment of HRQoL from a individual's point of view. Such measures are usually both individualised and preference-based, and two of them are of particular interest: The Schedule for the Evaluation of Individual Quality of Life (SEIQoL) [74], and the Extended Quality-Adjusted Time Without Symptoms and Toxicity (Q-TWIST) method [75]. The SEIQoL requires that patients nominate the five domains of most relevance to their quality of life. They then assess their current status within each domain using a visual analogue scale (VAS) with anchors ranging from "best possible" to "worst possible". Judgement analysis is used to rank the relative importance of each domain, based on patient ratings of 30 hypothetical quality of life scenarios for the five referenced domains. The SEIQoL generates an overall index that summarises satisfaction and relative importance of each domain. This approach is feasible although labour intensive as it requires in-person, semi-structured interviews and the provision feedback based on baseline data. The Extended Q-TWIST method is a special case of a number of techniques which use a quality-adjusted life-year (QALY) model based on individual patient-generated utilities at each point in time. In contrast to other preference-based approaches where patient importance ratings are elicited at one point in time, an Extended Q-TWIST requires collection of patient importance ratings over time for each quality of life domain and data on the social cost impact (e.g. work disability, institutionalisation) of a given disease and treatment. A weighted assessment score is computed which represents the severity of symptoms for each dimension, weighted by its patient-derived preference value. This score is then used to compute QALYs, which summarise the amount of healthy or quality time an individual patient experiences over the time of follow-up [76].

Differences have been demonstrated between clinician/nursing staff/spouse and patient ratings of patient HRQoL [77-88]. Generally, the observer gives a more pessimistic judgement
of patient HRQoL than does the patient. However, patient as well as observer ratings are subject to several biases [89-91]. Thus, it has been suggested that when feasible, patient ratings of HRQoL should be combined with observer ratings since they provide complementary information [66]. It is essential for clinicians and nursing staff to be aware of possible disparities between their own and the patient's perception of HRQoL aspects when planning, performing, and evaluating care.

**HRQoL assessment**

When evaluating the appropriateness of a data collection instrument, its reliability and validity should be carefully considered [92, 93]. HRQoL data may be collected by interviews or questionnaires. Interviews are seldom used in clinical trials since they are time-consuming and require extensive resources. Questionnaires are easier to apply to large populations, and many have been developed in the last 15 years. The questionnaires can be divided into generic and disease-specific. A modular approach, i.e. a basic general questionnaire supplemented by diagnosis- and/or treatment-specific modules has been recommended [94, 95] in cancer quality of life research.

It is important to choose an appropriate questionnaire for each specific HRQoL study. No instruments have been developed specially for the assessment of HRQoL in patients with endocrine GI tumours. The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) was selected as the main HRQoL measure for the present study. It is multidimensional, cancer-specific, reliable, valid, and sensitive to changes in HRQoL over time [96, 97]. The EORTC QLQ-C30 covers physical, social and psychological functioning as well as cancer-specific symptoms. It can be combined with disease-specific modules. However, no such module is available for patients with endocrine GI tumours. The EORTC QLQ-C30 has a strong focus on physical functioning and clinical symptoms [98]. It has been demonstrated that anxiety and depression are the most prevalent emotional reactions in cancer patients [99]. The Hospital Anxiety and Depression Scale (HADS) was developed to provide clinicians as well as researchers with a reliable, valid and practical tool for identifying the two most common forms of psychological disturbance in
somatically ill patients \cite{100, 101}. The HADS has been used in a large number of studies \cite{101}, and has been found to give clinically meaningful results as a screening tool for anxiety and depression. However, neither the EORTC QLQ-C30 nor the HADS deal with issues such as the meaning of illness, feelings of isolation, relationship with others, fears and hopes. It has been suggested that such aspects can assume great importance to patients \cite{77, 102-104} although they are not directly related to disease and treatment. It has also been suggested that feelings of uncertainty and fear of one's own mortality are major reasons for distress to cancer patients \cite{105}.

Data on HRQoL for the general population can be used as a guideline for the interpretation of scores from patient populations \cite{106}. EORTC QLQ-C30 data are available for the Swedish general population \cite{107}.

**HRQoL in patients with endocrine GI tumours**

Treatment of endocrine GI tumours is seldom curative. However, improved diagnostic and therapeutic methods have prolonged life for many of these patients. The assumption that adding time adds value, may often, but not always, be correct.

Few reports have been published in which HRQoL, anxiety and depression have been addressed in patients with endocrine GI tumours, and most of these do not address self-reported HRQoL. However, Jacobsen and Hanssen \cite{108} investigated HRQoL in eleven patients with endocrine GI tumours, in a comparison of the effects of octreotid with placebo, in a blinded cross-over study. Half of the patients received octreotid 100 µg twice daily for one month followed by placebo for one month, while the other half commenced with placebo followed by octreotid in a similar fashion. The Psychosocial Adjustment to Illness Scale \cite{109} was used to assess HRQoL. The results demonstrated that two quality of life domains, ability to relate socially and psychosocial distress, were significantly improved during therapy compared to placebo. Wymenga and co-workers \cite{110} investigated HRQoL in patients with endocrine GI tumours longitudinally during six months of therapy with lanreotide 30 mg every two weeks, using the EORTC QLQ-C30 for HRQoL assessment. After one month of
therapy, emotional and cognitive functions as well as global health status were significantly improved, and problems with fatigue, diarrhoea and insomnia had decreased significantly. However, only diarrhoea remained significantly improved after six months of therapy. In that study, the results were compared to population-based norms. At baseline, all ratings were below the ratings for the general population. O'Toole and co-workers [111] investigated differences in the ratings of HRQoL between patients treated with short-acting and long-acting somatostatin analogues in a cross-over study. Half of the patients received octreotid 200 µg two or three times daily for one month followed by lanreotide 30 mg every 10 days for one month, while the other half commenced with lanreotide followed by octreotid in a similar fashion. The Nottingham Health Profile [112] was used to measure HRQoL. The results demonstrated no significant differences in the ratings of HRQoL between the two treatment groups. As different assessment times as well as different HRQoL instruments were used in the above mentioned studies [108, 110, 111], no general conclusions can be drawn about HRQoL in patients with endocrine GI tumours. Levels of anxiety and depression in patients with endocrine GI tumours have been investigated in two studies [86, 87] with a cross-sectional design, using the HADS. The findings indicated low levels of anxiety as well as depression.

The handling of a demanding situation is often referred to as coping, i.e. cognitive and behavioural efforts to manage a difficult situation [113]. These efforts may moderate the effects of stress. Research on coping with cancer has identified a variety of specific strategies, most of which may be classified as confrontative or avoidant [114]. The overarching goal of coping research is to identify which specific coping strategies are best for managing problems and distressing emotions. The above mentioned studies of HRQoL [108, 110, 111], anxiety and depression [86, 87] in patients with endocrine GI tumours indicate that these patients experience a relatively good quality of life and low levels of anxiety and depression. This relatively good psychosocial function may reflect that patients are successful in handling disease- and treatment-related problems. However, little is known about which strategies patients with endocrine GI tumours use for coping or to "keep a good mood" in spite of their disease and treatment, and even less is known about how they handle specific disease- and treatment-related problems.
Taken together, patients with GI tumours, present specific symptoms of disease and side-effects of treatment, and often have a long survival. Little is known about how these patients perceive their HRQoL, how much anxiety and depression they experience, and how they handle disease- and treatment-related problems. The present study is designed to investigate HRQoL and the psychosocial function of patients with endocrine GI tumours.
AIMS OF THE THESIS

The aim was to investigate HRQoL in patients with endocrine GI tumours in order to broaden the understanding of the psychosocial function of these patients. Such knowledge is vital in order to give these patients the best possible care. The specific aims were:

1. To assess patient perceptions of the importance of and satisfaction with selected HRQoL aspects (I, II, III).
2. To investigate possible differences between patient and staff perceptions of the importance of selected HRQoL aspects (I).
3. To investigate possible differences and/or associations between patient and staff perceptions of (a) patient satisfaction with HRQoL aspects, and (b) patient anxiety and depression (I).
4. To investigate whether patient ratings of HRQoL are related to importance and/or satisfaction ratings of selected HRQoL aspects (II).
5. To investigate whether patient ratings of HRQoL are related to importance-satisfaction discrepancies in the ratings of HRQoL aspects (II, III).
6. To investigate patient ratings of HRQoL among subgroups of patients: (a) anxiety/depression "cases" vs "noncases" (II), and (b) groups formed on the basis of background variables (II, III).
7. To investigate whether patient ratings of HRQoL, anxiety and depression change during one year of treatment with α-INF and/or a somatostatin analogue (IV).
8. To compare patient ratings of HRQoL with HRQoL in the Swedish general population (IV).
9. To investigate possible relations between on the one hand patient ratings of HRQoL, anxiety and depression, and on the other, levels of biochemical tumour markers (IV).
10. To investigate the credibility of earlier results concerning the psychosocial function of patients with endocrine GI tumours, especially patients with carcinoid tumours. This was done by inductively identifying patient and staff perceptions of (a) common types of disease- and treatment-related distress among patients with carcinoid tumours, and (b) what constitutes a good quality of life for patients with carcinoid tumours (V).
11. To identify which strategies patients with endocrine GI tumours use to "keep a good mood" in spite of disease and treatment (V).
METHODS

Sample
All patients included in Studies I-V are patients referred for medical treatment to the Section of Endocrine Oncology, Department of Internal Medicine at the Uppsala University Hospital. Staff members from this section were included in Studies I and V.

Patients were eligible if they were diagnosed with a histopathologically verified endocrine GI tumour, and had been informed about their diagnosis. They were excluded if they did not speak and read Swedish, and/or were considered by their physician to be in a too bad mental, physical or emotional condition.

Specific exclusion criteria for patients were:
Study I: patients were excluded if they had not been treated with $\alpha$-INF and/or a somatostatin analogue for at least one month prior to data collection, and if they had a stay of less than two days on the ward at the time of the data collection.
Study II: patients were excluded if they had not been treated with $\alpha$-INF and/or a somatostatin analogue for at least one month prior to data collection, and if they were currently undergoing chemotherapy.
Study III: patients were excluded if they had the diagnosis for less than five years.
Study IV: patients were excluded if they did not have a carcinoid tumour, were not scheduled for treatment with $\alpha$-INF and/or a somatostatin analogue, if they had been treated with chemotherapy and/or a biological response modifier during the last month, or were scheduled for additional treatment with chemotherapy.
Study V: patients were excluded if they did not have a carcinoid tumour, had had their diagnosis for less than one month or longer than five years, had not been treated with $\alpha$-INF and/or a somatostatin analogue for at least four weeks prior to the data collection, had been treated with chemotherapy, had a stay on the ward of less than two days at the time of data collection, and/or participated in another HRQoL study.

See Table 1 for a presentation of the characteristics of patients included in Studies I-V.
**Study I**

Sixty patients were eligible. Twelve were excluded [did not speak Swedish (n=4), stay of less than two days on the ward (n=8)]. One patient declined participation, and in 30 cases, it was impossible to pair the patient with a staff member according to the procedure. This left 17 patients for the study.

All registered nurses (n=12) and nurse assistants (n=5) working regular hours on the ward were asked to participate and none declined. Mean age was 45 years (range 30-58) and all were female. The mean time they had worked on the ward was 72 months (range 2-262).

**Study II**

Two-hundred and twelve patients were eligible. One-hundred and one were excluded [did not speak Swedish (n=13), too bad mental, physical or emotional condition (n=4), treated with chemotherapy (n=84)]. Eleven patients did not participate due to administrative failure and one patient declined. This left 99 patients for the study.

**Study III**

One-hundred and sixty-one patients were eligible. Twelve were excluded [did not speak Swedish (n=4), too bad mental, physical or emotional condition (n=8)]. Twenty-eight declined participation and two did not participate due to administrative failure. This left 119 patients for the study.

**Study IV**

Thirty-four patients were eligible. Ten were excluded [did not speak Swedish (n=3), concomitant chemotherapy (n=1), prior treatment with α-INF/somatostatin analogue (n=6)]. This left 24 patients for the study. Six patients did not complete the study due to death (n=3)
Table 1. Patient characteristics.

<table>
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<th>Study I (n=17)</th>
<th>Study II (n=99)</th>
<th>Study III (n=119)</th>
<th>Study IV (n=24)</th>
<th>Study V (n=19)</th>
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<td>9/8</td>
<td>60/39</td>
<td>67/52</td>
<td>14/10</td>
<td>13/6</td>
</tr>
</tbody>
</table>
or treatment termination (n=3). In addition, at two assessment points (6 and 9 months) there was attrition due to administrative failure, which left the following number of participants at follow-up: 3 months n=21, 6 months n=17, 9 months n=16, and 12 months n=18.

**Study V**
Fifty-six patients were eligible. Fourteen were excluded [too bad mental, physical or emotional condition (n=1), concomitant chemotherapy (n=1), included in another research study (n=3), a stay of less than two days on the ward (n=9)]. Twenty-three were not approached as it was impossible to pair the patient with a staff member according to the procedure. This left 19 patients for the study.

All registered nurses (n=11) and nurse assistants (n=4) working regular hours on the ward were asked to participate and none declined. Two nurses and two nurse assistants participated twice. Mean age was 48 years (median 50, range 28-61) and all were female. The mean time they had worked on the ward was 92 months (median 72, range 6-304).

**Instruments**
An overview of the instruments used in the different studies is presented in Table 2.

Table 2. Overview of instruments used in Studies I-V.

<table>
<thead>
<tr>
<th>Instruments</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic background sheet</td>
<td>I X</td>
</tr>
<tr>
<td>Disease- and treatment-related questions</td>
<td>II X</td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>III X</td>
</tr>
<tr>
<td>HADS</td>
<td>IV X</td>
</tr>
<tr>
<td>KPS</td>
<td>V X</td>
</tr>
<tr>
<td>Importance of HRQoL</td>
<td>X X</td>
</tr>
<tr>
<td>Satisfaction with HRQoL</td>
<td>X X</td>
</tr>
<tr>
<td>Semistructured interview questions</td>
<td>X X</td>
</tr>
</tbody>
</table>
Background data
Patients completed questions concerned with socio-demographic (age, gender, civil status, if they had children or not, occupational status) and medical (diagnosis, time since diagnosis, type of treatment, number of hospitalisations for the present illness) background facts in all studies.

Biochemical tumour markers
Plasma levels of chromogranin A (reference range <4\(\mu\)g per liter), and the urine serotonin metabolite, 5-hydroxyindoleacetic acid (U-5HIAA) (reference range <80 \(\mu\)mol per 24 hours), were used as biochemical tumour markers.

HRQoL, anxiety and depression
The EORTC QLQ-C30 (version 2.0) \[^96\] was used to study patient judgement of HRQoL. The EORTC QLQ-C30 is designed to cover a range of HRQoL issues relevant to a broad spectrum of cancer patients. It has been found to exhibit adequate levels of reliability and validity and the psychometric properties are consistent across languages and countries \[^96, 115-117\]. The validity of the EORTC QLQ-C30 is satisfactory also when used with long-term cancer survivors \[^118\]. The EORTC QLQ-C30 is composed of the following multi-item measures: five functional scales: physical (PF), role (RF), cognitive (CF), emotional (EF), and social (SF), three symptom scales: fatigue (FA), pain (PA), and nausea/vomiting (NV), one global health status/quality of life scale (QL), and six single-item measures: dyspnoea (DY), appetite loss (AP), sleeping problems (SL), constipation (CO), diarrhoea (DI), and financial problems (FI). A one-week time frame is employed. In accordance with the scoring instructions given by the EORTC Quality-of-Life Study Group \[^96\], the scale scores are linearly transformed to 0-100 scores. For the functional, global health and overall quality of life scales, a higher score means a higher level of functioning. For the symptom-oriented scales and items, a higher score corresponds to a higher level of symptoms. The questionnaire can be completed without assistance in a relative short time by most patients.
Physical function was measured by the Karnofsky Performance Status Scale (KPS) \cite{119} which is an observer rating scale that has been frequently used to evaluate the physical function of somatically ill patients. It is an 11-point numerical scale, ranging from normal functioning (100) to death (0). The KPS has been found to have adequate reliability and validity \cite{120}.

Some disease- and treatment-related questions were used to assess the occurrence and intensity of the most common symptoms among patients with endocrine GI tumours treated with $\alpha$-INF and somatostatin analogues. In Studies I and II, patients were asked to report whether they had experienced diarrhoea and/or flush the previous week, using the following response format: "not at all"; "some"; "quite a bit" and "very much". Further, they were asked to report how often they received help to take their injections: "never"; "sometimes"; "often" and "always". In Study IV, patients were asked to report whether they had experienced flush, muscle pain, fever or dry skin. In Study IV, the data used for the analysis were obtained by transforming response alternatives into scores as follows: "not at all" = 1, "some" = 2, "quite a bit" = 3, and "very much" = 4.

The HADS \cite{100} was employed to investigate patient judgement of anxiety and depression. It is designed to assess anxiety and depression in somatically ill patients. The HADS consists of two subscales, one measuring anxiety (seven items) and the other depression (seven). Each item has four possible answers, with scores from zero, indicating no problem, to three indicating a high level of problems (lowest possible total score = 0, highest possible total score = 21). There is no single, generally accepted cut-off score for the HADS. In the original study, Zigmond and Snaith recommended two cut-off scores for both subscales: 7/8 for possible and 10/11 for probable anxiety or depression \cite{100}. In the present thesis, a cut-off score of $\geq 8$ has been used. The HADS has been extensively used in patients with different, mostly somatic, diseases including cancer and it has been found to have sufficient reliability and validity \cite{101}. The Swedish version \cite{121} has been considered to be fit for use among patients with different types of cancer \cite{81, 122, 123}. 

In addition to the original HADS, a "staff version" [85] was used to investigate staff judgement of patient anxiety and depression. This version consists of exactly the same items as those posed to patients, except that the questions are directed to the staff asking them to reply as they think the patient responded to each item. Satisfactory values for internal consistency have been demonstrated [86] for the staff version.

**Importance of HRQoL aspects**

VAS (anchors: "Very important" and "Not at all important") were used to investigate the importance of twelve HRQoL aspects as judged by patients and staff. The aspects were chosen to cover the most common problems experienced by this group of patients according to our clinical experience. Patients and staff were asked: "To experience a good quality of life, how important is it to...?". Six questions concerned physical HRQoL aspects: "Wash yourself, dress, eat etc.", "Do physical exercise", "Have a good health", "Not have pain", "Not have diarrhoea", and "Not have flush". Six questions dealt with HRQoL aspects of a more social nature: "Associate with the family", "Associate with friends", "Go to a movie, theatre, exhibition etc.", "Watch TV, listen to the radio, read books etc.", "Work", and "Do every-day household jobs". Patients and staff were asked to indicate their opinion on the 10 cm VAS. The score used for the data analysis was obtained by measuring the number of cm from the "Not at all important" anchor. This instrument was constructed for the present project and no psychometric data are available.

**Satisfaction with HRQoL aspects**

VAS (anchors: "Very satisfied" and "Not at all satisfied") were used to investigate patient satisfaction with twelve HRQoL aspects. A one-week time frame was employed. Patients were asked "How satisfied are you with ...?" and staff were asked "How satisfied do you think the patient is with...?". The HRQOL aspects and the scoring procedure were the same as those employed to study the importance of HRQOL aspects. The instrument was constructed for this project and no psychometric data are available. Respondents were first asked to rate the importance of each aspect and thereafter to rate the patient's satisfaction with each item.
Three scales and one item in the EORTC QLQ-C30 (QL, PA, DI, PF) correspond thematically to some of the HRQoL aspects (Have a good health, Not have pain, Not have diarrhoea, Do physical exercise) which were investigated for importance and satisfaction. To explore the relations between, on the one hand importance-satisfaction discrepancies, and on the other ratings of EORTC QLQ-C30, patients were classified in two groups: those who had higher importance than satisfaction ratings and those who had equal or higher satisfaction than importance ratings for each of the four corresponding HRQoL aspects.

Psychosocial function in patients with endocrine GI tumours
To investigate the credibility of earlier results concerning the psychosocial function of patients with endocrine GI tumours, and to identify which strategies patients use to "keep a good mood", semi-structured interviews with open-ended questions were conducted. The interviews were audiotaped and transcribed verbatim. Patients and staff members were asked the following questions (in the same order): 1) Is there anything, with regard to disease and treatment, that is distressing to you/that you think is distressing to the patient at the moment?, 2) What, if anything, has been most distressing for you/do you think has been most distressing for the patient, with regard to disease and treatment, since the time when you/the patient became ill?, 3) What is important for you/do you think is important for the patient to perceive that you have/the patient has a good quality of life? and 4) What do you do/do you think the patient does to "keep a good mood" in spite of disease and treatment? The interviews were conducted individually in a secluded part of the ward. The same interviewer interviewed all participants. The interviews ranged from 20 to 60 minutes, and interviews with patients generally took longer than those conducted with staff members.

Procedures
All studies were approved by the Research Ethics Committee of the Faculty of Medicine, Uppsala University. In Studies I, II, IV and V, patients were given oral and written information, and in Study III written information, about the study. In Studies I and V, staff members were given oral information on two separate occasions. Informed consent was obtained from all participants.
Study I
When a patient had agreed to participate, he or she was randomly paired to a nurse or nurse assistant who had taken care of him/her for at least two days. The pairing procedure was done by the ward head nurse, who blindly drew a staff name from a box. Staff members were paired to only one patient each. Instructions on how to use the instruments were given to each patient and staff member by the author. The author was present when the patient completed the instrument. Staff members completed the instruments on their own. Patients and staff gave their replies on the same day.

Study II
When a patient had agreed to participate, he or she was instructed, by the author, in how to complete the questionnaires. The author was present when the patient completed them.

Study III
Patients were identified through the patient register at the Section of Endocrine Oncology. The questionnaires were mailed to patients with a written consent form and a stamped return envelope. The questionnaires were to be returned to the Department of Public Health and Caring Sciences. A reminder was sent if the patient did not reply within one month.

Study IV
When a patient had agreed to participate, he or she was instructed, by the author, in how to complete the questionnaires. The author was present when the patient completed them. Biochemical tumour markers were assessed at the Section of Endocrine Oncology on the day before treatment start (baseline), and at approximately 3, 6, 9 and 12 months after treatment start.

Study V
When a patient had agreed to participate, he or she was randomly paired to a nurse or nurse assistant who had taken care of him/her for at least two days. The pairing procedure was done by the author, who blindly drew a staff name from a box. After agreement to participate, patients as well as staff were presented a written version of the interview questions. This was
done a few days before the interview in order to give participants a possibility to reflect on their experiences and perceptions related to the interview questions. At the time of data collection, patients as well as staff first answered questions about demographic characteristics. Thereafter, a semi-structured interview with open-ended questions was performed, patients and staff were interviewed separately. The interviewer was supportive and follow-up questions were sometimes asked in order to make the participants elucidate or develop their answers. The interviews were audiotaped and transcribed verbatim by the interviewer.

**Data analysis**

Statistical methods used in Studies I-IV are presented in Table 3.

<table>
<thead>
<tr>
<th>Test</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>$\chi^2$-test</td>
<td></td>
</tr>
<tr>
<td>One sample t-test</td>
<td></td>
</tr>
<tr>
<td>Paired t-test</td>
<td>X</td>
</tr>
<tr>
<td>Unpaired t-test</td>
<td></td>
</tr>
<tr>
<td>Mann-Whitney-U test</td>
<td></td>
</tr>
<tr>
<td>Pearson product moment coefficient</td>
<td>X</td>
</tr>
</tbody>
</table>

**Questionnaire data**

$\chi^2$-tests were employed for the assessment of associations between dichotomised variables. One sample t-tests were used (a) to investigate whether ratings of HRQoL, anxiety and depression and scores for biochemical tumour markers at 3, 6, 9 and 12 months after treatment start differed from those before treatment start, and (b) to investigate whether ratings of HRQoL differed from expected scores for healthy Swedish adults. The comparisons between patient ratings of the EORTC QLQ-C30 and Swedish norm data [107] were made after adjustment for age and gender. This was done by obtaining expected mean scores, using the Swedish population reference scores for each age and gender group [124]. A difference of >10 between an observed and an expected value, was used as it has been suggested [116, 125]
that a change of >10 points on the EORTC QLQ-C30 may be considered clinically worthwhile. Paired t-tests were used to compare patient perceptions of the importance of and satisfaction with selected HRQoL aspects. Unpaired t-tests were used (a) to investigate whether background variables had any relation to ratings of HRQoL, anxiety and depression, (b) to compare patient and staff ratings of patient satisfaction with HRQoL aspects, anxiety and depression, (c) to investigate whether subgroups, based on anxiety/depression ratings differed in their ratings of HRQoL, and (d) to investigate whether subgroups based on importance-satisfaction discrepancies differed in their ratings of HRQoL. The Mann-Whitney U-test was used to investigate possible differences between patients and staff in their ratings of the importance of HRQoL aspects. Pearson product moment coefficients were used to test for (a) associations between patient ratings of HRQoL and background variables, (b) associations between on the one hand HRQoL, anxiety and depression ratings, and on the other, scores on biochemical tumour markers, and (c) associations between patient and staff ratings of patient satisfaction with HRQoL, anxiety and depression.

The software used was StatView 5.0 SAS Institute Inc. 1992-1998, for Macintosh.

Interview data

Interview data were analysed using content analysis [126]. This method may be used to draw valid conclusions about a manifest message in a communication by objective and systematic identification of specified communication characteristics [127]. Words and sentences in the interviews were classified into categories which were supposed to reflect central messages. Sentences which were classified in the same category were presumed to have a similar meaning, either based on the precise meaning of the words or on words sharing similar connotations.

The content analysis was performed in the following steps: 1. The transcribed text was read and the manifest statements by each individual in response to each of the interview questions were identified. 2. Sentences and parts of sentences that contained information relevant to the research questions were identified and defined as recording units. 3. Recording units were grouped into mutually exclusive categories reflecting central text messages. These three steps
were performed by the author. After a discussion between the author and two other persons, some categories were judged to be misleading, and were therefore rewritten. Boundaries of each category were defined and descriptions of the central characteristics of each category were developed. Categories were thereafter grouped into dimensions according to their content (by the author together with two other persons). No matter how many times a certain recording unit was mentioned by a patient or a staff, it was calculated as mentioned once by that specific person in the presentation of the results.

**Interrater agreement for categories.** With access to the recording units, the categories and the descriptions of the central characteristics of each category, a second independent assessor (a fourth person) assigned the recording units to the categories. Boundaries between categories and their content were discussed (by the author and two other persons) and a few changes were performed in order to clarify the coding system and categories. Finally, a comparison of the assessors' categorisations of statements was done with the Kappa (κ) method [128]. The κ values for categories varied between 0.80 and 0.97.

**Respondent validation.** To ensure that the experience of having carcinoid tumours had been fully described, on the basis of the replies to the interview questions, three patients and three staff members were asked to review and reflect upon the categories generated. This brought forth five new categories, four with regard to distress (Bother by changed sexual activity, Worry before diagnosis, Worry about not having access to the best possible care in the future, Worry about not knowing the doctor) and one concerned with strategies to "keep a good mood" (Seeking information about disease and treatment). When rereading the interviews, eight patient and three staff statements, not previously categorised, were identified and categorised as Worry before diagnosis. One patient and one staff statement regarding sex life was identified, and categorised as Bother by changed sexual activity. No statements were identified that could be referred to the remaining three new categories.
RESULTS

Summaries of Studies I-V

Study I: Quality of life in patients with endocrine tumors of the gastrointestinal tract: patient and staff perceptions.

The EORTC QLQ-C30 data show that patients assigned high scores to the functional scales, and that EF was given the lowest score (M=76, sd=25). The results for the symptom scales and single items demonstrate that patients reported most problems with fatigue (M=41, sd=22), dyspnoea (M=33, sd=26) and diarrhoea (M=31, sd=28). In response to the disease- and treatment-related questions, 65% reported that they had at least some problems with diarrhoea during the last week, and 59% reported that they had "some" flush. One third stated that they at least sometimes during the last week needed help with their injections. A minority considered their family life and/or social life to be affected by diarrhoea, flush and/or taking injections.

Table 4 shows patient mean values and sd:s for the perceived importance of and satisfaction with the 12 selected HRQoL aspects. Significant mean value differences between patient importance and satisfaction ratings were found for four aspects: Not have diarrhoea (t=3.04, df=16, p<0.01), Have a good health (t=2.83, df=16, p<0.05), Not have pain (t=2.16, df=16, p<0.05), and Do physical exercise (t=2.78, df=16, p<0.05). For all of these, the importance rating was higher than the satisfaction rating.

Table 5 illustrates staff mean values and sd:s for their ratings of perceived importance of and estimated patient satisfaction with the same aspects. There was one significant mean value difference between patient and staff importance ratings: staff rated Work as more important in order to experience a good quality of life, as compared to patients (t=2.43, df=32, p<0.05). There were no significant ranking differences regarding the importance of the HRQoL aspects between patients and staff.
Table 4. Patient mean values and sd:s for the perceived importance of and satisfaction with twelve HRQoL aspects, Studies I, II and III.

<table>
<thead>
<tr>
<th>Quality of life aspect</th>
<th>Study I (n=17)</th>
<th>Study II (n=99)</th>
<th>Study III (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Importance</td>
<td>Satisfaction</td>
<td>Importance</td>
</tr>
<tr>
<td></td>
<td>Mʰ</td>
<td>sd</td>
<td>Mʰ</td>
</tr>
<tr>
<td>Wash yourself, dress, eat etc.</td>
<td>9.8</td>
<td>0.4</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>9.6</td>
<td>0.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Do physical exercise</td>
<td>8.4</td>
<td>2.5</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>5.7</td>
<td>4.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Have a good health</td>
<td>9.5</td>
<td>1.3</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
<td>3.1</td>
<td>6.4</td>
</tr>
<tr>
<td>Not have pain</td>
<td>8.9</td>
<td>1.6</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>3.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Not have diarrhoea</td>
<td>9.2</td>
<td>1.5</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>4.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Not have flush</td>
<td>7.0</td>
<td>3.7</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>8.8</td>
<td>1.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Associate with the family</td>
<td>9.0</td>
<td>2.0</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>8.7</td>
<td>2.0</td>
<td>8.9</td>
</tr>
<tr>
<td>Associate with friends</td>
<td>7.5</td>
<td>3.4</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
<td>2.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Go to a movie, theatre, exhibition etc.</td>
<td>5.8</td>
<td>3.4</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>6.6</td>
<td>3.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Watch TV, listen to the radio, read a</td>
<td>8.1</td>
<td>2.5</td>
<td>8.1</td>
</tr>
<tr>
<td>book etc</td>
<td>8.8</td>
<td>1.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Work</td>
<td>5.5</td>
<td>4.5</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>3.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Do every-day household jobs</td>
<td>8.7</td>
<td>2.5</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>8.1</td>
<td>3.1</td>
<td>8.1</td>
</tr>
</tbody>
</table>

ᵃHighest possible value=10, lowest possible value=0,
Table 5. Staff mean values and sd:s for perceived importance of and ratings of patient satisfaction with twelve quality of life aspects.

<table>
<thead>
<tr>
<th>Quality of life aspect</th>
<th>Importance</th>
<th>Patient satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M^a</td>
<td>M^a</td>
</tr>
<tr>
<td>Wash yourself, dress, eat etc.</td>
<td>9.6 1.0</td>
<td>9.4 0.7</td>
</tr>
<tr>
<td>Do physical exercise</td>
<td>7.3 2.3</td>
<td>5.0 3.3</td>
</tr>
<tr>
<td>Have a good health</td>
<td>9.6 0.8</td>
<td>4.6 2.8</td>
</tr>
<tr>
<td>Not have pain</td>
<td>9.7 0.5</td>
<td>6.6 3.4</td>
</tr>
<tr>
<td>Not have diarrhoea</td>
<td>9.2 1.5</td>
<td>5.0 3.2</td>
</tr>
<tr>
<td>Not have flush</td>
<td>9.0 1.8</td>
<td>6.4 3.1</td>
</tr>
<tr>
<td>Associate with the family</td>
<td>9.8 0.4</td>
<td>8.6 1.5</td>
</tr>
<tr>
<td>Associate with friends</td>
<td>8.2 1.6</td>
<td>6.8 1.8</td>
</tr>
<tr>
<td>Go to a movie, theatre, exhibition etc.</td>
<td>6.4 3.3</td>
<td>4.9 2.8</td>
</tr>
<tr>
<td>Watch TV, listen to the radio, read books etc.</td>
<td>8.5 1.7</td>
<td>7.9 2.3</td>
</tr>
<tr>
<td>Work</td>
<td>8.6 2.4</td>
<td>5.0 3.3</td>
</tr>
<tr>
<td>Do every-day household jobs</td>
<td>8.1 2.8</td>
<td>6.8 3.3</td>
</tr>
</tbody>
</table>

^a Highest possible value=10, lowest possible value=0

Patients gave higher absolute mean satisfaction ratings than did staff to all HRQoL aspects, and the ratings differed significantly for 4/12 aspects: Not have flush (t=2.87, df=15, p<0.01), Have a good health (t=3.34, df=15, p<0.01), Associate with friends (t=2.35, df=15, p<0.05), and Work (t=2.30, df=15, p<0.05). There was a significant positive correlation between patient and staff ratings regarding Associate with the family (r=0.62, df=15, p<0.01).

There were no significant mean differences or correlations between patient and staff ratings of patient anxiety and depression. Patient ratings indicated five "cases" of anxiety, only one of these was recognised as such by the staff. Staff rated six patients as anxiety "cases", one of these rated himself as a "case". Patient ratings indicated two depression "cases", none of these was recognised as such by the staff. Staff rated two patients as depression "cases".

In sum, patients reported a relatively good HRQoL, and reported most problems with fatigue, dyspnoea and diarrhoea. There were no major differences between patients and staff regarding perceptions of the importance of selected HRQoL aspects. Staff gave a more pessimistic view of patient satisfaction with HRQoL than did patients, and staff did not accurately judge individual patients' levels of anxiety and depression. Thus, patient-staff agreement on patient HRQoL could be improved. In addition, it seems important to get more
knowledge about the relationship between the perceived importance of and satisfaction with these issues.

**Study II: Health-related quality of life in patients with endocrine tumours of the gastrointestinal tract.**

The EORTC QLQ-C30 data show that patients assigned high scores to the functional scales, and that RF was given the lowest score (M=71, sd=29). The results for the symptom scales and single items demonstrate that patients reported most problems with fatigue (M=39, sd=26), dyspnoea (M=35, sd=29) and diarrhoea (M=32, sd=33). In response to the disease- and treatment-related questions, 62% reported that they had at least some problems with diarrhoea during the last week and 39% stated that they had at least some flush. One third stated that they at least sometimes during the last week needed help with their injections. A minority considered their family life and/or social life to be affected by diarrhoea, flush and/or taking injections.

Table 4 illustrates patient mean values and sd:s for the perceived importance of and satisfaction with the 12 selected HRQoL aspects.

Patients' perceived importance ratings did not match their satisfaction ratings for some of the selected HRQoL aspects. For two aspects, the satisfaction rating was significantly higher than the importance rating: Not have flush (t=2.8, df=94, p<0.01) and Watch TV, listen to radio, read books etc. (t=2.8, df=98, p<0.01). For four aspects, the importance rating was significantly higher than the corresponding satisfaction rating: Do physical exercise (t=4.2, df=97, p<0.001), Have a good health (t=8.7, df=98, p<0.01), Not have pain (t=4.6, df=98, p<0.001), and Not have diarrhoea t=4.0, df=98, p<0.001).

For the importance/satisfaction aspects for which there was a thematically corresponding EORTC QLQ-C30 scale/item, there were few significant correlations. There was a significant correlation between the EORTC QLQ-C30 rating and the importance rating for Have a good health/QL (r=0.23, df=88, p<0.05). Similarly correlations were obtained between the EORTC
QLQ-C30 rating and the corresponding satisfaction rating for Do physical exercise/PF (r=0.40, df=87, p<0.001), Have a good health/QL (r=0.74, df=88, p<0.001), Not have pain/PA (r=-0.83, df=88, p<0.001) and Not have diarrhoea/DI (r=-0.76, df=88, p<0.001).

The subgroup with a higher importance than satisfaction rating had a lower rating of two of the corresponding EORTC QLQ-C30 functional scales (PF t= 3.1, df=96, p<0.01; QL t=6.3, df=97, p<0.001) than the group with equal or higher satisfaction ratings. The subgroup with higher importance ratings also had significantly higher ratings on the corresponding EORTC QLQ-C30 symptom scales (PA t=8.3, df=97, p<0.001; DI t=7.2, df=97, p<0.01) than the group with equal or higher satisfaction ratings. Thus, importance>satisfaction discrepancies may identify patients with low quality of life.

Levels of anxiety (M=4.6, sd=3.9) and depression (M=3.6, sd=3.1) were low. Nineteen patients scored at or above the anxiety "cut-off point" and 13 scored above the depression "cut-off point". Among these, nine patients scored as anxiety and depression "cases". Significant differences were found between anxiety "cases" and "non-cases" for nine EORTC QLQ-C30 scales/items (RF, EF, CF, SF, QL, FA, PA, SL, FI) and between depression "cases" and "non-cases" for ten scales/items (PF, RF, EF, CF, SF, QL, FA, NV, PA, DY).

Throughout, "non-cases" had higher functions and fewer symptoms than "cases". Anxiety "cases" were less satisfied with four of the selected HRQoL aspects than were "non-cases", and depression "cases" were less satisfied with eight aspects than were "non-cases". The group with higher importance than satisfaction ratings on the twelve HRQoL aspects reported higher levels of anxiety and/or depression.

Few significant differences were obtained between subgroups formed on the basis of demographic and medical background variables, and there was no systematic pattern.

Patient scores on the EORTC QLQ-C30 scales were lower on the functional scales and higher on the symptom scales compared to healthy Swedish adults of similar age and gender (Table 6).
To sum up, patients reported a relatively good HRQoL and low levels of anxiety and depression. Further, they reported most problems with fatigue, dyspnoea and diarrhoea which corroborates the findings of Study I. For four aspects, patient satisfaction did not match the perceptions of importance of the same aspect. With one exception, there were no associations between HRQoL ratings and perceived importance of the same issue, but some associations between the HRQoL ratings and ratings of satisfaction. Importance>satisfaction discrepancies may identify patients with a low quality of life. Anxiety or depression "caseness" indicated a lower level of function, a higher level of problems and lower satisfaction with HRQoL, whereas background variables were not related to these ratings. Patients evidenced a lower HRQoL compared to healthy people of similar age and gender.

**Study III:** *Importance-satisfaction discrepancies are associated with health-related quality of life in five-year survivors of endocrine gastrointestinal tumours.*

The EORTC QLQ-C30 data show that patients assigned high scores to the functional scales, and that RF was given the lowest score (M=77, sd=25). The results for the symptom scales and single items demonstrate that patients reported most problems with fatigue (M=34, sd=26), diarrhoea (M=31, sd=36) and dyspnoea (M=25, sd=31).

Patient mean values and sd:s for the perceived importance of and satisfaction with 12 selected HRQoL aspects are shown in Table 4. The importance ratings were significantly higher than the satisfaction ratings for the majority of the twelve selected HRQoL aspects: Wash yourself, dress, eat etc. (t=2.2, df=110, p<0.05), Do physical exercise (t=5.9, df=109, p<0.001), Have a good health (t=9.1, df=108, p<0.001), Not have pain (t=5.9, df=104, p<0.001), Not have diarrhoea (t=6.1, df=103, p<0.001), Associate with the family (t=3.9, df=108, p<0.001),
Table 6. Expected (population based) and observed scores for the EORTC QLQ-C30 scales and single items, Studies II, III and IV (baseline).

<table>
<thead>
<tr>
<th>EORTC QLQ-C30 scale</th>
<th>Study II (n=99)</th>
<th>Study III (n=119)</th>
<th>Study IV (baseline, n=24)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Observed scores</td>
<td>Expected scores</td>
<td>Obs-Exp difference</td>
</tr>
<tr>
<td>MM D M M D M M D</td>
<td>M M M D</td>
<td>M M M D</td>
<td>M M M D</td>
</tr>
<tr>
<td>Physical functiona</td>
<td>77 88 -11****</td>
<td>79 87 -8****</td>
<td>85 85 0</td>
</tr>
<tr>
<td>Role functiona</td>
<td>80 88 -8***</td>
<td>82 88 -6**</td>
<td>83 88 -5</td>
</tr>
<tr>
<td>Emotional functiona</td>
<td>80 88 -8***</td>
<td>82 88 -6**</td>
<td>83 88 -5</td>
</tr>
<tr>
<td>Cognitive functiona</td>
<td>80 88 -8***</td>
<td>82 88 -6**</td>
<td>83 88 -5</td>
</tr>
<tr>
<td>Social functiona</td>
<td>80 88 -8***</td>
<td>82 88 -6**</td>
<td>83 88 -5</td>
</tr>
<tr>
<td>Global health/quality of lifea</td>
<td>67 77 -10***</td>
<td>65 76 -11***</td>
<td>68 76 -8</td>
</tr>
<tr>
<td>Fatigueb</td>
<td>39 20 +19***</td>
<td>34 21 +13***</td>
<td>36 21 +15**</td>
</tr>
<tr>
<td>Nausea/vomitingb</td>
<td>8 3 +5***</td>
<td>6 3 +3**</td>
<td>19 3 +16**</td>
</tr>
<tr>
<td>Painb</td>
<td>26 19 +7*</td>
<td>19 20 -1</td>
<td>19 20 +1</td>
</tr>
<tr>
<td>Dyspneab</td>
<td>35 17 +18***</td>
<td>25 18 +7*</td>
<td>19 19 0</td>
</tr>
<tr>
<td>Insomniab</td>
<td>22 17 +5</td>
<td>24 18 +6*</td>
<td>24 19 +5</td>
</tr>
<tr>
<td>Appetite lossb</td>
<td>16 4 +12****</td>
<td>10 4 +6**</td>
<td>25 4 +21**</td>
</tr>
<tr>
<td>Constipationb</td>
<td>8 5 +3</td>
<td>6 5 +1</td>
<td>15 6 +9</td>
</tr>
<tr>
<td>diarrhoeab</td>
<td>32 5 +27***</td>
<td>31 5 +26***</td>
<td>46 6 +40***</td>
</tr>
<tr>
<td>Financial difficultiesb</td>
<td>20 7 +13****</td>
<td>18 7 +11***</td>
<td>6 6 0</td>
</tr>
</tbody>
</table>

*aScores range from 0 to 100, a higher score representing a higher level of function, bScores range from 0 to 100, a higher score representing a higher level of symptoms.

*p<0.05, **p<0.01, ***p<0.001
Associate with friends \((t=2.0, \text{df}=112, p<0.05)\), Work \((t=3.0, \text{df}=56, p<0.05)\) and Do every-day household jobs \((t=4.0, \text{df}=106, p<0.001)\).

The subgroup with a higher importance than satisfaction rating reported a lower HRQoL for three of the corresponding EORTC QLQ-C30 scales/items (QL \(t=6.2, \text{df}=106, p<0.001\); PA \(t=7.4, \text{df}=101, p<0.001\); DI \(t=7.4, \text{df}=101, p<0.001\)) than the did the group with an equal or higher satisfaction rating. With a few exceptions (diagnosis, treatment), demographic and medical background variables did not contribute to the explanation of the differences in ratings between the two importance-satisfaction subgroups.

Few significant differences were obtained in the EORTC QLQ-C30 ratings between subgroups formed on the basis of demographic or medical background variables. Younger patients \((\leq 50 \text{ years})\) \((M=29, \text{sd}=32)\) reported more pain than did older patients \((M=17, \text{sd}=24)\) \((t=2.0, \text{df}=117, p<0.05)\). Further, age was related to the ratings of HRQoL (EF \(r=0.20, \text{df}=117, p<0.05\); SF \(r=0.21, \text{df}=117, p<0.05\); FI \(r=-0.22, \text{df}=117, p<0.05\); PA \(r=-0.18, \text{df}=117, p<0.05)\).

Patient scores on the EORTC QLQ-C30 scales indicated a lower HRQoL compared to healthy Swedish adults of similar age and gender (Table 6).

To sum up, patients reported a relatively good HRQoL, and most problems with fatigue, dyspnoea and diarrhoea which strengthens the findings in Studies I and II. Patients whose ratings of the importance were higher than their ratings of satisfaction with the same aspect also evidenced a low HRQoL for that aspect. Background variables were not related to HRQoL ratings. Patients evidenced a lower HRQoL than did healthy people of similar age and gender. This pattern of findings is similar to that of Study II.
Study IV: Quality of life, anxiety and depression in patients with carcinoid tumours during the first year of treatment with α-interferon and/or a somatostatin analogue.

At baseline, patients reported a relatively good quality of life with the EORTC QLQ-C30 scales, and RF was the functional scale that was given the lowest score (M=65, sd=33). Patients reported most problems with diarrhoea (M=46, sd=39), appetite loss (M=25, sd=34), and sleep disturbance (M=24, sd=35). There were few significant changes in the ratings of HRQoL, anxiety and depression during the first year of treatment. Significant mean differences were found for two EORTC QLQ-C30 scales. The score for PF was lower at 6 (D=-21) (t=3.2, df=16, p<0.01), 9 (D=-18) (t=2.3, df=15, p<0.05) and 12 months (D=-20) (t=3.9, df=17, p<0.01) compared to baseline. Similarly, the score for NV was lower at 12 months (D=-9) (t=2.6, df=17, p<0.05). The score for flush was lower at 9 (D=-0.6) (t=2.4, df=16, p<0.05) and 12 months (D=-0.6) (t=2.7, df=17, p<0.05) compared to baseline, as was the rating for fever at 3 months (D=-0.3) (t=2.6, df=20, <0.05). The score for muscle pain was higher at 12 months (D=+0.5) (t=3.0, df=17, p<0.01) as was the score for dry skin (D=+0.6) (t=2.4, df=17, p<0.05). The score for HADS anxiety was lower at 12 months (D=-1.9) (t=2.3, df=17, p<0.05) and the score for depression was higher at 9 months (D=+1.8) (t=2.4, df=17, p<0.05) compared to baseline.

Patient ratings of HRQoL (EORTC QLQ-C30) differed from the expected scores for healthy Swedish adults of similar age and gender, both before treatment start (Table 6) and after 12 months. At 12 months the observed-expected difference were significant for PF, SF, QL, FA and DI. These differences were more than 10 points below (PF, SF, QL) or above (FA, DI) the expected value and may thus be of potential clinical relevance. Thus, patients evidenced a lower HRQoL compared to healthy people of similar age and gender before treatment start as well as after 12 months.

The levels of tumour markers did not change in a major way. Few relations were demonstrated between on the one hand ratings of HRQoL, anxiety and depression, and on the other biochemical tumour markers. However, the ratings of diarrhoea at 12 months were positively associated with plasma chromogranin A (r=0.48, p<0.05) and U-5HIAA (r=0.68,
p<0.01). Also, the depression ratings at 12 months were positively associated with plasma chromogranin A (r=0.51, p<0.05).

In sum, patients reported a relatively good HRQoL at baseline, which accords with the findings in Studies I-III. The ratings of HRQoL, anxiety and depression did not change substantially during the first year of treatment. Patients evidenced a lower HRQoL compared to healthy people before treatment start, as well as 12 months later which corroborates the findings from Studies II and III.

**Study V: Distress, quality of life and strategies to "keep a good mood" in patients with carcinoid tumours: patient and staff perceptions.**

Twenty-five categories concerned with disease- and treatment-related distress were developed on the basis of the interview data. The categories were grouped in three dimensions. Physical dimension: Appetite loss, Diarrhoea, Discomfort in joints/muscles, Dry skin/mucous membranes, Dyspnoea, Fatigue, Flush, Insomnia, Nausea, and Pain-abdomen; Emotional dimension: Bother by changed appearance, Bother by changed sexual activity, Depression, Irritation, Troublesome tests/examinations, Worry before check-up, Worry before diagnosis, Worry that the family can't cope with the illness, Worry that the illness will get worse, Worry that the illness will interfere with ability to care for husband/wife; and Social dimension: Limited possibility/ability to associate with friends, Limited possibility/ability to dine out, go to concerts, theatre etc., Limited possibility/ability to perform physical activities, Limited possibility/ability to travel, and Limited possibility/ability to work/pursue daily activities.

The most frequently mentioned statements by patients were categorised as Fatigue and Diarrhoea, (Physical), Worry before diagnosis, Worry that the illness will get worse (Emotional), and Limited possibility/ability to perform physical activities (Social). Statements most frequently mentioned by staff were categorised as Fatigue, Diarrhoea, Appetite loss (Physical), Worry that the illness will get worse and Worry before check-up (Emotional).

Ten categories concerned with quality of life aspects were developed from the interview data and these were grouped in three dimensions. Physical: Good appetite, Health, Not
experiencing fatigue, Not experiencing pain in the abdomen and Not having diarrhoea; Emotional: Good appearance; and Social: Associate with family and friends, Live one's life in accordance with one's desire, Pursue hobbies/leisure time activities, and Work and pursue daily activities.

The most frequently mentioned statements by patients were categorised as Pursue hobbies/leisure time activities, Associate with family and friends, Live one's life in accordance with one's desire, and Work and pursue daily activities. All these categories were judged to belong to the Social dimension. Staff most frequently mentioned statements categorised as Associate with family and friends, Pursue hobbies/leisure time activities and Live one's life in accordance with one's desire, judged to belong to the Social dimension, and Not experiencing fatigue, judged to belong to the Physical dimension.

Nine categories were developed from the interview data in response to the question "What do you do/do you think the patient does to "keep a good mood" in spite of disease and treatment?" The categories were grouped in two dimension: Internal strategies: Accepting, Ignoring disease- and treatment-related distress, Keeping active, Keeping a positive view of life, and Making downward comparisons; and External strategies: Getting emotional support from the family, Getting emotional support from friends, Getting good care, and Getting tangible support from the family. Patients and staff most frequently mentioned statements categorised as Keeping active, Keeping a positive view of life and Accepting. These were judged to belong to the Internal dimension.

Fourteen categories developed from the interview data about disease- and treatment-related distress and important aspects of quality of life are not covered by the EORTC QLQ-C30: Bother by changed appearance, Bother by changed sexual activity, Discomfort in joints/muscles, Dry skin/mucous membranes, Flush, Good appearance, Limited possibility/ability to travel, Living one's life in accordance with one's desire, Pain-abdomen, Troublesome tests/examinations, Worry before check-up, Worry that the family can't cope with the illness, Worry that the illness will get worse, and Worry that the illness will interfere with the ability to care for the husband/wife. The following two quality of life categories are
not covered by the EORTC QLQ-C30: Good appearance and Living one's life in accordance with one's desire.

The interview data about distress revealed eight specific fears and worries not covered by the HADS: Bother by changed sexual activity, Irritation, Troublesome tests/examinations, Worry before check-up, Worry before diagnosis, Worry that the family can't cope with the illness, Worry that the illness will interfere with the ability to care for husband/wife, and Worry that the illness will get worse.

In conclusion, the results suggest areas of distress and important quality of life aspects (a) to be monitored by staff as potentially distressing for patients with carcinoid tumours, and (b) to be included in future studies of the psychosocial function of these patients. The identified aspects are mostly covered by the EORTC QLQ-C30 and the HADS. However, some issues were identified concerning worry and restrictions regarding social activities that are not included in the EORTC QLQ-C30 or the HADS. Thus, the findings in Studies I-IV regarding HRQoL, anxiety and depression seem to be credible, but in order to get a better understanding of the psychosocial function of this patient group, the instruments should be complemented in some respects. In response to the question about what patients do to "keep a good mood", Getting good care was identified, thus indicating a possible and potentially important relation between the quality of care and patients' HRQoL.
GENERAL DISCUSSION

Patients with endocrine GI tumours is an interesting population for quality of life studies for several reasons: they present specific symptoms of disease and treatment, they have a relatively long survival and are kept under continued surveillance by specialist units for many years, and new treatment options are continuously developed.

HRQoL, anxiety and depression among patients with endocrine GI tumours

Patients with endocrine GI tumours report a relatively good quality of life, and low levels of anxiety and depression. They experience most problems with physical aspects, not unexpectedly diarrhoea and fatigue. These aspects were also the two most often mentioned categories of physical distress when patients and staff were asked to freely express what disease- and treatment-related distress patients with endocrine GI tumours experience. However, no conclusions can be drawn about the degree to which these categories are problematic and/or important. Participants were asked to mention aspects of disease and treatment they perceived as distressing but were not asked to state the frequency, intensity or importance of the problem. Low levels of emotional and social/role problems were reported with the HADS and the EORTC QLQ-C30, and a minority of the patients considered having diarrhoea, flush and taking injections to affect their family or social life. When patients freely expressed what was distressing, several emotional as well as social aspects were identified. Among the emotional aspects, Worry that the illness will get worse was mentioned most frequently. This issue has been identified in earlier research, and it has been suggested [105, 129] that feelings of uncertainty and fear of one's own mortality are major areas of distress for cancer patients. Slevin et al [78] have suggested that cancer patients are anxious and worried chiefly because of worry about their future. Worry before diagnosis was identified as a distressing aspect. This result is worth extra consideration in this group of patients since the diagnosis of an endocrine GI tumour is rare and it often takes a long time before the patient gets the final diagnosis. During this time, the patient often meets doctors and nursing staff that cannot answer his/her questions which may create uncertainty and worry. All freely expressed social aspects of distress were related to restricted possibilities/abilities to perform activities, caused by disease or treatment e.g. appetite loss, diarrhoea, fatigue and taking injections. Role function (which includes questions about restrictions to perform hobbies and work) was the EORTC QLQ-C30 functional scale with the lowest scores. Taken together, the results indicate
that physical distress is not only problematic in itself but may have a social implications for these patients.

Long-term survivors of endocrine GI tumours seem to enjoy a better physical and emotional HRQoL, as compared to patients closer to diagnosis. This result may reflect positive effects of employed therapies and/or good care, but may also be influenced by patient adjustment to and acceptance of their situation.

Anxiety and depression ratings were low, which accords with earlier results [86, 87]. In a meta-analytic review of the psychological sequelae of a cancer diagnosis [130] it was shown that, as a group, cancer patients do not experience more psychological distress than the normal population or other medically ill patients. However, the findings do not imply that psychological distress is absent among patients with cancer, but suggest that the relatively low distress ratings of most patients are a result of successful adaptation to their disease experiences.

There were no significant mean value differences between patient and staff ratings of patient anxiety and depression. However, staff did not accurately judge individual patients’ levels of anxiety and depression. This finding is in line with results from previous studies among cancer patients [85, 86]. There are several possible explanations for this mismatch between ratings, and one of them may be insufficient communication between patients and staff. Also, there may be a difference between the way cancer patients rate their experience and what they "really experience", since cancer patients have been reported to withhold signs of emotional distress from their staff [131, 132]. Further, it has been suggested that staff capabilities to identify what is troublesome for the patient are limited [133-135], and staff have reported feelings of inadequacy in communicating with cancer patients [136, 137]. The results underline the importance of an effective patient-staff communication, and the need of training programs for staff, including training in communication skills, to probe information disclosed by patients about their perceptions of their illness or prognosis or any adverse physical, psychological or social sequelae of their disease and treatment.
Anxiety and depression "cases" reported a lower HRQoL than "non-cases" on the EORTC QLQ-C30 and the satisfaction scales. Similar results have been reported [138-141]. The direction of influence, if any, between anxiety/depression and HRQoL cannot be determined from the present data. However, the results imply that determination of HADS "caseness" yields information about which patients run a risk of a low overall HRQoL.

Neither demographic nor medical background variables seem to be useful for identifying subgroups with a low HRQoL. However, in the group of long-time survivors, younger patients (≤50 years) reported a lower HRQoL than older patients with regard to both emotional and social function and a more negative economical impact. Thus, young age (≤50 years) seems to identify patients who need more support with respect to psychosocial function. There were no major differences in HRQoL between patients with carcinoid tumours and EPT in the group of long-time survivors, but patients with carcinoid tumours reported more diarrhoea and less pain and sleeping problems than patients with EPT. The significant differences between patients treated with α-INF and patients treated with α-INF and a somatostatin analogue after 12 months of treatment are clinically interesting. The group treated with both agents rated their overall quality of life (QL) higher and problems with sleep (SL) lower compared to the group treated with α-INF only. The group treated with both agents rated anxiety lower than did to those treated with α-INF only. The number of patients in Study IV was very small and the findings should be interpreted with caution, however, the results indicate that the group treated with both agents experience less problems than those treated with α-INF only.

In terms of statistical significance, the ratings of HRQoL, anxiety and depression did not change substantially during the first year of treatment, and the observed changes were both for the worse (PF, muscle pain, dry skin, depression) and for the better (NV, flush, fever, anxiety). There were few changes of >10 points, considered as clinically worthwhile for the EORTC QLQ-C30 ratings. For fever and depression, a change was observed at one assessment point, at 3 and 9 months respectively, but at 12 months the difference was not significant. The deterioration of muscle pain, dry skin and depression may be explained by side-effects of the employed therapy, since they are known side effects of α-INF. The change
of NV and flush may reflect a positive effect of the employed therapies even if the changes were not accompanied by significant changes in tumour markers.

Those aspects of HRQoL that were significantly deteriorated after 12 months of treatment were of a physical character, while emotional aspects were not impaired, and the level of anxiety actually changed for the better. The emotional function reported at baseline was significantly lower than that expected for people of similar age and gender. However, after one year this difference was no longer significant. This suggests that these patients may be successful in handling the emotional demands of their disease and treatment even if physical symptoms aggravate. These findings are similar to those of another study of HRQoL in patients with endocrine GI tumours [108], in which it was reported that psychosocial distress was reduced during treatment with octreotid.

In the process of understanding how patients with endocrine GI tumours perceive their HRQoL, the present HRQoL findings were compared to data from studies of other patient groups. Such comparisons are not readily interpreted because of differences in symptomatology, treatment and time of survival. A comparison between the present HRQoL results and previous results from reports concerning HRQoL in patients with endocrine GI tumours [108, 110, 111] is unfeasible, since different assessment points and different HRQoL instruments have been used in the different studies. In one of these studies [110] the findings at baseline were compared to population-based norms, however, the findings were not age and gender matched, and the norm-data was based on a sample of women only. Further, in these studies patients were treated with somatostatin analogues but not interferon. A comparison of patient scores on the EORTC QLQ-C30 with expected scores for the Swedish general population yielded an estimate of the HRQoL of this patient group compared to healthy people. The comparison revealed that these patients perceived a lower HRQoL than expected for healthy people of similar age and gender.

It has been suggested [108] that levels of tumour markers and symptoms are reflected in the ratings of HRQoL in patients with endocrine GI tumours. This could not be proven in the present study, since few relations were demonstrated between tumour markers and the ratings of HRQoL, anxiety and depression. Both chromogranin A and U-5HIAA were associated
with ratings of diarrhoea. This result is expected since serotonin is involved in the mechanism regulating diarrhoea [142]. The lack of significant associations suggests that levels of tumour markers do not reflect HRQoL. However, these findings may be related to the fact that the results are based on data from a small sample.

Neither the EORTC QLQ-C30 nor the HADS have been developed for the purpose of assessing HRQoL, anxiety or depression of patients with endocrine GI tumours. The content validity of these instruments for that purpose can therefore be questioned. However, most of the categories developed from the interview data about distress are covered by the EORTC QLQ-C30. In addition, the interview data revealed several emotional aspects of distress that are not included in the EORTC QLQ-C30. These aspects as well as social restrictions ought to be paid attention to when the psychosocial function of patients with endocrine GI tumours is investigated. When the EORTC QLQ-C30 is used to investigate the psychosocial function in the patient group, it should be complemented in these respects. Although the disease-specific, modular-approach has been recommended for the EORTC QLQ-C30 [94], at present, no such module is available for patients with endocrine GI tumours. Several emotional aspects that emerged from the interview data are not covered by the HADS, which may be due to the fact that the HADS does not focus on specific emotional aspects but is designed to assess general anxiety and depression.

**Perceptions of the importance of and satisfaction with HRQoL**

It can be argued that tools should only include those aspects of quality of life that we reasonably well can expect to be influenced by disease and treatment [143]. However, it has been suggested that aspects such as the meaning of illness, isolation, fears and hope, can assume the same or greater importance to the patient as may issues related to symptoms or physical functioning [102, 103]. When women with breast cancer were asked to rank HRQoL items according to importance, they ranked general health items such as self-care, mobility, physical activity and family relations higher than disease- or treatment-related items [144]. In accordance with this notion, the present results suggest that those aspects that are perceived as most important are not necessarily those that are most distressing. When patients and staff were asked about what is important in order for the patient to experience a good quality of life, they most frequently mentioned aspects of a social character. However, when asked to
mention aspects of disease and treatment that are distressing, they most often mentioned statements of a physical character.

It has been suggested that dissatisfaction with a particular ability will have a detrimental effect on well-being only to the extent that this ability is viewed as important [68]. It has been found [69] that the functions that mobility-disabled persons lacked most compared to the non-disabled were rated as less important by the disabled, and that disabled persons tend to de-emphasise functions related to health and mobility [71].

The twelve selected HRQoL aspects were supposed to cover the most common problems experienced by this group of patients. Therefore, it was expected that patients should report these aspects as important for a good quality of life. The ratings of satisfaction with these HRQoL aspects suggest that patients perceived their quality of life as at least relatively satisfactory. For most of the aspects, the importance rating was significantly higher than the satisfaction rating. This may be explained by the fact that most of the aspects were judged to be highly important and that the differences mainly reflect the high importance of an aspect. However, the significant differences are fairly equally distributed over most of the 0-10 importance scale, and only very few aspects are given a satisfaction rating below 6 on the 0-10 scale. The conclusion is that the differences reflect genuine importance-satisfaction discrepancies and not merely high importance ratings.

Patient ratings of importance were not associated with ratings of the corresponding EORTC QLQ-C30 scale/item. This result supports findings of another study [141], in which 83 patients with endocrine GI tumours were asked to rate the "importance of", "satisfaction with" and "symptom/function of" selected HRQoL aspects. The results demonstrated few associations between ratings of the "importance of" and "satisfaction with" as well as between ratings of the "importance of" and "symptom/function of" the selected HRQoL aspects. The lack of correlations between the perceived importance of a quality of life aspect and the EORTC QLQ-C30 ratings may reflect that the aspects that are most important in order to perceive a good quality of life are not necessarily the same as those that are most distressing.
Patients who gave a higher importance than satisfaction rating to a specific HRQoL aspect also gave a lower rating to the corresponding EORTC QLQ-C30 scale/item than those with equal or higher satisfaction than importance ratings. These findings suggest that importance-satisfaction discrepancies are valid indicators of patient distress. However, the conclusion can be questioned as (a) the questions concerning importance and satisfaction were not exactly the same as the questions in the EORTC QLQ-C30, and (b) the response format for the importance/satisfaction questions was not the same as the response format for the EORTC QLQ-C30. However, in a recent study [141], where the response format was a VAS, and the items were the same for "importance of", "satisfaction with" and "symptom/function of" the selected HRQoL aspects, the pattern was the same. The group with higher importance than satisfaction ratings reported a worse HRQoL on more scales and single items than did the group with equal or higher satisfaction ratings. In addition, the result agrees with earlier findings [69, 145] demonstrating that life satisfaction is related to the discrepancy between the patients' perception of the importance and attainment of life values. Medical and demographic background variables could not explain the differences in EORTC QLQ-C30 ratings between the two importance-satisfaction subgroups.

In agreement with patients, staff perceived the selected HRQoL aspects to be important. This result may be due to the fact that staff had worked for a long time in hospital care and therefore had come to share some of the patients' opinions of what is important for a good quality of life. Patients and staff assigned the highest importance to aspects of a physical character. Only one significant difference was demonstrated between patient and staff importance ratings. This was for the aspect Work, and the most likely explanation is the fact that the majority of patients (10/17) did not work, seven of these were old age pensioners. As there were no major differences between patient and staff perceptions of the importance of the selected HRQoL aspects, no speculations are possible concerning the influence that staff evaluation of what is important for a good HRQoL may have had on their judgement of patient satisfaction with HRQoL.

Patients were more satisfied with some of the selected HRQoL aspects than staff perceived them to be. This result is in accordance with previous results [79, 82, 84-87, 146]. Taken together, the results indicate that staff perceive patients to be less satisfied and have a lower
HRQoL as compared to patient reports. This suggests that patient-staff communication requires specific knowledge and skills in the area of communication, for staff to accurately judge patient HRQoL.

**Strategies that patients with endocrine GI tumours use to "keep a good mood"
**

Most of the categories developed from the responses to the question about what the patient does to "keep a good mood" agree with the available literature about how patients with cancer handle their situation [114], the identified strategies could be classified as confrontative or avoidant. However, Getting good care has previously not been reported as a strategy to "keep a good mood". This result indicates a possible and potentially important relation between "good care" and/or patient satisfaction with care and the well-being of patients with cancer. It has recently been found that patient satisfaction with nurses' communication skills and doctors' interpersonal skills is related to well-being among patients with endocrine GI tumours [147]. It is known that relationships with other people may promote human strength [148], and there is evidence demonstrating that good patient-centred communication is associated with good psychosocial function among cancer patients [149]. It has also been suggested [105, 134] that improvements in the communication of doctors with patients can significantly enhance patients' understanding of their disease, their psychological adjustment, and possibly survival outcomes. It is reasonable to believe that good care contributes to the patients' efforts to manage the situation and "keep a good mood" in spite of disease and treatment.

No conclusions can be drawn on the basis of the present results about how (a) patients "keep a good mood" with regard to specific disease- and treatment-related problems, or (b) whether a certain patient uses the same or different strategies to "keep a good mood" for all disease- and treatment-related problems.

**Methodological limitations and considerations
**

One methodological limitation in Studies I, II, III and V is the cross-sectional design that prevents conclusions concerning whether (a) HRQoL, anxiety and depression differ with time since diagnosis, (b) importance-satisfaction discrepancies are predictive of later HRQoL, (c)
HADS "caseness" is predictive of later HRQoL, and whether (d) the strategies patients use to "keep a good mood" vary over time.

The patient groups in Studies I-III are heterogeneous with regard to diagnosis, treatment and time since diagnosis, which may limit the value of a single point of HRQoL assessment. However, the data revealed very few differences with regard to HRQoL, anxiety and depression related to medical background variables.

A large number of comparisons have been performed in Studies I-IV. This increases the risk of significant results arising by chance. This may be handled by using the Bonferroni correction \[^{[128]}\]. However, this method of correction results in conservative tests, causing an over-correction of type I errors \[^{[150]}\]. A specific reason for not using the Bonferroni correction in the present studies is the small sample sizes, which could further increase the risk for over-correction of type I errors. However, a p-level of <0.01 for statistical significance was chosen in Study II to reduce the chance of false positive results. It is important to exercise caution in the interpretation of p-values when there is a large number of comparisons, and multiple, correlated endpoints.

Study IV suffers from the small sample size, and in addition, there is the problem of attrition. These circumstances may have contributed to the lack of statistically significant findings. Longitudinal quality of life studies in advanced-stage cancer unfortunately produce substantial non-random missing data due to death and deteriorating health. It has been pointed out that a failure to recognise the problem of such missing data can lead to overestimates of patient HRQoL, which may even suggest a palliative effect of treatment \[^{[151]}\]. Patients who are not doing well the last time they contributed data are not represented in a complete case analysis approach. To overcome this difficulty, the calculation of difference score at each assessment point relative to baseline ratings was chosen as the method for analysis of the data in Study IV. This method does not exclude those patients who have a progressive disease, severe side-effects or who have died.

The method of pairing patients and staff in Studies I and V limited the number of patients that could be included. However, this is not considered to be a threat to the external validity of the
findings since the exclusion of patients was not systematic. In addition, the results from Study I support the findings from earlier studies investigating patient and staff perceptions of patient distress [85, 86].

In Studies I and V, staff were asked about various aspects of patients' psychosocial function. The usefulness of asking staff about patients' psychosocial function may be questioned since discrepancies between patient and staff ratings have been reported in these matters [78, 79, 82, 83, 85, 146]. However, neither patient nor staff ratings can be considered to be perfectly reliable [90, 152] and it can be questioned whether the patient or the staff rating is "the valid" measure. In the present study, the solution to this problem has been to investigate the phenomena from two angles, from patients' and staff's points of view.

The method for data collection in Study V gave the participants a possibility to freely express their perceptions. Two assessors separately read, analysed and categorised the data. There was good agreement between the assessors' categorisations, which points to the credibility of the results. In order to achieve a rich set of data, participants were presented the interview questions a few days before the interview. This was done with the purpose to provide them with an opportunity to reflect on their experiences and perceptions. The trustworthiness of the content analysis was supported by a validation of the findings with respondents.

Conclusions
The main conclusion is that patients with endocrine GI tumours perceive a relatively good quality of life.

1. Patient ratings of the importance of and satisfaction with selected HRQoL aspects do not match for the majority of aspects.

2. There are no major differences between patient and staff perceptions of the importance of selected HRQoL aspects.

3. Staff give a more pessimistic view of patient satisfaction with HRQoL aspects than do patients, and staff does not accurately judge individual patients' levels of anxiety and depression.

4. Patient ratings of HRQoL are not related to importance ratings of HRQoL aspects. However, for the same aspects, patient ratings of HRQoL are related to their satisfaction ratings.
5. Higher ratings of "importance of" as compared to "satisfaction with" a specific HRQoL aspect are indicative of a low HRQoL.

6. Anxiety and depression "cases" experience a lower HRQoL than do "non cases". Background variables are not related to HRQoL.

7. Ratings of HRQoL, anxiety and depression do not change substantially during the first year of treatment with α-INF and/or a somatostatin analogue.

8. Patients evidenced a lower HRQoL than was expected for an age- and gender-matched sample of the Swedish general population.

9. Levels of biochemical tumour markers do not correspond with ratings of HRQoL, anxiety and depression.

10. Earlier results concerning HRQoL, anxiety and depression in patients with endocrine GI tumours seem to be credible. However, in order to get a better understanding of these patients' psychosocial function the instruments that have been used (the EORTC QLQ-C30, the HADS) should be complemented in some respects, mainly with issues concerning worry and restrictions regarding social activities.

11. Getting good care was one of the identified strategies to "keep a good mood", indicating a possible and potentially important relation between the quality of care and the patients' HRQoL.

This project have provided knowledge about areas of distress and important quality of life aspects to patients with endocrine GI tumours and these should be investigated not only in terms of presence and degree, but also in terms of importance and satisfaction. The findings have also highlighted the potential importance of a good quality of care to improve the patients' quality of life.
IMPLICATIONS AND FUTURE DIRECTIONS

The results provide information about those aspects of distress and quality of life that should be monitored by staff as potentially distressing/important for patients with endocrine GI tumours. Further, the results could provide the basis for development of an instrument assessing the psychosocial function of patients with endocrine GI tumours. Such an instrument could be helpful in exploring not only the occurrence and intensity of potentially distressing aspects, but also their perceived importance as well as what strategies patients use to "keep a good mood" with regard to the same aspects. It would be useful to use such an instrument to explore these aspects at various times during the patients' illness trajectory.

Future research should focus on the relations between on the one hand biochemical tumour markers, and on the other patients' HRQoL, and the extent to which biochemical tumour markers are predictive for future HRQoL. Subgroups with a lower HRQoL have been identified. These are patients with a higher importance than satisfaction rating for certain HRQoL aspects and patients with high levels of anxiety or depression. It should be investigated whether these factors are predictive of future HRQoL.

Since neither medical (diagnosis, time since diagnosis, treatment) nor demographic (age, gender) background variables are related to HRQoL, it is of importance to find out more about which factors are related to HRQoL. The quality of care, the patient's hope and social support may be such factors.

A potentially important relation between good care and the well-being of patients with cancer was identified. This relation ought to be explored in a study using a prospective design to investigate whether different care activities e.g. those that define nurses' communication skills and doctors' interpersonal skills have an impact on patient well-being.
ABBREVIATIONS

α-INF  α-interferon
AP      appetite loss
CF      cognitive function
CO      constipation
DI      diarrhoea
DY      dyspnoea
EF      emotional function
EORTC QLQ-C30 the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EPT     endocrine pancreatic tumours
FA      fatigue
FI      financial impact
GI      gastrointestinal
HADS    the Hospital Anxiety and Depression Scale
HRQoL   health-related quality of life
κ       kappa
KPS     the Karnofsky Performance Status Scale
NV      nausea/vomiting
PA      pain
PF      physical function
QALY    quality adjusted life year
QL      global health-status/quality of life
Q-TWIST Quality-adjusted Time Without Symptoms and Toxicity
RF      role function
SEIQoL  the Schedule for Evaluation of Individual Quality of Life
SF      social function
SL      insomnia
U-5HIAA urine-5-hydroxyindoleacetic acid
VAS     visual analogue scale
WHO     the World Health Organization
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REFERENCES

80. Sprangers, MA and Aaronson, NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. *J Clin Epidemiol.* 1992; 45: 743-60.


141. Larsson, G, Sjödén, PO and von Essen, L. Relations between ratings of "importance of", "satisfaction with", and "symptom/function of" quality of life aspects as well as well-being. *Manuscript*.
147. von Essen, L, Larsson, G, Öberg, K and Sjödén, PO. "Satisfaction with care": associations with health-related quality of life, and psychosocial function among Swedish patients with endocrine gastrointestinal tumours. *Submitted for publication*.

ERRATA

**Paper I**

Table 1, 3 and 4  
"interact with family" should be "associate with the family"
"visit with friends" should be "associate with friends"
"do every-day household chores" should be "do every-day household jobs"
"physical exercise" should be "have physical exercise"

Table 2  
"Appetite" should be "appetite loss"

Table 3  
"^d p<005." should be "^d p<0.05."

**Paper II**

Page 485, first column, line 15  
"df=96, p<0.01" should be moved to line 20, right behind $t=3.1$

Page 498, first column, line 11  
Reference no (10) should be (11)

Table 4  
"Appetite" should be "Appetite loss"

**Paper III**

Page 1322, first column, line 50  
"appetite" should be "appetite loss"

Page 1323, second column, line 9  
"r=0.18" should be "r=-0.18"

Page 1323, second column, line 10  
"r=0.22" should be "r=-0.22"