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Health-Related Quality of Life in Patients with Small Intestine Neuroendocrine Tumours

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Short running title: Quality of Life in Patients with SI-NET

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Abstract

Background: The prevalence of small intestine neuroendocrine tumours (SI-NETs) is increasing. Disease progression is often slow and treatment options and long-term survival rates have improved, but little is known about health-related quality of life (HRQoL) in these patients.

Objective: To assess HRQoL and its predictors in SI-NET patients receiving contemporary treatments.

Methods: We measured HRQoL with 15D and SF-36 questionnaires in 134 SI-NET patients and compared the 15D results to those of age- and gender-standardized general population (n = 1153). In the patients, we studied impact of treatments, Ki67, liver metastases, circulating tumour markers, comorbidities and/or socioeconomic factors on HRQoL with linear regression analysis.

Results: Mean disease duration of the patients was 81 (4-468) months, 91% had metastatic disease and 79% received somatostatin analog treatment. Hepatic tumour load was 0% in 44.8%, <10-25% in 44.0%, and >25% in 11.2%, respectively. Mean fP-CgA and S-5HIAA concentrations were 15 (1.3-250) nmol/l and 344 (24-7470) nmol/l, respectively. Overall HRQoL was significantly impaired in patients compared to controls (15D scores 0.864±0.105 vs 0.905±0.028, p<0.001). SI-NET patients scored worse on 9 of 15 dimensions (sleep, excretion (ie bladder and bowel function), depression, distress, vitality, sexual activity (p< 0.001), breathing, usual activities, and discomfort and symptoms (p< 0.01-0.05). SF-36 scores were impaired and highly correlated with 15D scores (p<0.001). HRQoL was impaired in patients with (n=85) compared to patients without (n=49) impaired excretion (0.828 vs 0.933, p<0.001). In the patient group, number of medications predicted impaired HRQoL.

Conclusions: Despite contemporary treatments, SI-NET patients have severely impaired HRQoL, including diarrhea, sleep, depression, vitality and sexual activity.

Introduction

Small intestine neuroendocrine tumours (SI-NETs) arise from neuroendocrine cells in the jejunum or ileum and typically secrete bioactive peptides. Currently, increasing incidences in the range of 0.5-1.5 per 100.000 inhabitants and year are reported [1-4]. Most tumours are grade 1 and 2, defined by a Ki67 index of ≤2% and 2-20%, respectively [5]. They are characterized by relatively slow tumour progression and long overall survival [1]. Surgery is the cornerstone of treatment and advancements in systemic treatment options, including somatostatin analog and interferon therapy, everolimus, and peptide receptor radionuclide therapy (PRRT) have further improved survival rates in patients with SI-NETs. SI-NETs commonly produce serotonin and, when metastasized to the liver, patients may develop carcinoid syndrome including diarrhea, flushing, bronchospasm and, in the advanced stage, cardiac valvular fibrosis and right-sided heart failure. [6]

Reports of improved survival rates indicate that important therapeutic goals have been achieved for this patient group. The somatostatin analogs octreotide and lanreotide efficiently improve symptoms of diarrhea and flushing. In selected patients, debulking of liver metastases, ablative therapies and other liver-directed modalities may also relieve symptoms and hormonal overproduction. Quality of life is considered an important measure of patients' perception of the burden of their disease and the impact of treatment modalities. Despite this, data on health-related quality of life (HRQoL) in patients with SI-NETs are scarce.

In this study, we compare HRQoL in a cohort of carefully characterized SI-NET patients from a single center, and compare the results to those of a large sample of the general population. Within the patient group, we searched for predictors of HRQoL.

Patients and Methods

Subjects

Patients. Patients with a histologically confirmed diagnosis of SI-NET treated at the Division of Endocrinology and Department of Oncology, Helsinki University Hospital (HUH) during year 2017 were invited to participate in the study. Because all patients operated on for neuroendocrine tumours are referred either to the Endocrinology or Oncology unit at HUH. These subjects represent the majority of/all SI-NET patients in the HUH area. Only patients with available data on pathologic, radiologic and biochemical parameters were included. We identified a total of 211 subjects from our electronic patient records with the diagnosis of SI-NET or carcinoid syndrome (ICD-codes E17.9 or E34.0). Thirty subjects were excluded from the study. Of them, ten had another severe disease (cognitive impairment, severe heart failure due to other cause than carcinoid heart, other malignancy) and two were in palliative care. Six subjects had deceased within the year. Clinical data was not available for twelve subjects who had been referred to our multidisciplinary NET tumour board for consultation.

An invitation letter, the 15D and the SF36 questionnaires, and a supplementary questionnaire (Supplementary questionnaire) were sent in June 2017 to 181 patients identified from our electronic patient records. An additional letter was sent to all non-responders within 4-6 weeks. Biochemical and clinical data,comorbidities (cardiovascular disease, diabetes, depression which were taken into account if a patient was taking a medication for them) were retrieved from our electronic patient records. Pathology reports were collected from the electronic patient records.

Control population. The results obtained with the 15D instrument were compared to those of a large age- and gender-standardized sample of the Finnish general population from the Finnish Health 2011 survey (n=1153) [7]. This sample was from the same catchment area as the patients.

Ethics

The study was approved by the ethics committee of Helsinki University Hospital. All patients gave their signed informed consent for participation in the study.

HRQoL Assessment

The 15D questionnaire is a generic, standardized, well-validated, self-administered measure of HRQoL for persons aged 16 or more [8]. 15D was chosen as it also measures the dimension of excretion, in contrast to SF-36, and as the results could be compared to those of a large age- and gender-standardized general population. The 15D proved to be the best generic HRQoL instrument regarding sensitivity and construct validity in a study by Richardson et al., comparing six different generic tests, including the SF-6 [9]. The 15D can be used both as a profile and a single score measure. The questionnaire consists of 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion (includes both bladder and bowel function), usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each dimension is divided into five levels and respondents choose the level best describing their current health status (for the 15D questionnaire, see Supplementary data). The 15D score and the dimensional level values (on a 0-1 scale) are calculated from the health state descriptive system by using a set of population-based preference or utility weights. This allows calculation of the 15D score representing the overall HRQoL. A higher score reflects a better HRQoL. The minimum important change for the 15D score is estimated to be ±0.015 and 0.015 can also be regarded as the minimum clinically important cross-sectional difference between groups [10].

The SF-36 is a questionnaire measuring self-reported HRQoL in 8 dimensions: physical functioning, role limitations due to physical health, role limitations due to emotional problems, vitality, mental health, social functioning, bodily pain and general health. HRQoL scores are presented on a 0-100 scale. A higher score indicates better HRQoL. [11]

In addition, the patients answered a short supplementary questionnaire (Supplementary questionnaire, see Supplementary data) including questions on marital status, educational level, symptoms (diarrhea, flushing, abdominal pain, defecation frequency) and regular medication.

Assessment of hepatic tumour burden

An experienced radiologist (R.L) re-assessed hepatic tumour burden of the SI-NET patients who answered the questionnaires employing CT (98 patients), MRI (28 patients), or ^{68}Ga-Dotanoc PET/CT (8 patients) if no CT or MRI scans were available. Tumour burden was estimated using a visual semi-quantitative approach. This method has previously been applied in other studies on patient with NETs [12,13]: 4-6 scan slices with the most extensive affection were selected and scored visually for the extent of the disease. In case of multiple scans of the same patient, we chose the scan timely closest to the date of the HRQoL questionnaires. Hepatic tumour burden was divided into five categories: 0%, <10%, 10-25%, 25-50% and >50%.

Laboratory Measurements

All laboratory analyses, including serum 5-hydroxyindoleacetic acid (S-5HIAA) were performed at the Helsinki University Hospital Laboratory, HUSLAB, using in-house methods. Plasma chromogranin A (fP-CgA) was measured by radioimmunoassay. S-5HIAA was measured by liquid chromatography – mass spectrometry [14].

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics 24 for Windows. Independent samples t-test was used to test the statistical significance of the differences in the means between SI-NET patients and controls

from the general population. Independent samples t-test was also used to evaluate the impact of a single determinant (age, gender, educational level, use of somatostatin analog, hepatic metastases, fP-CgA level, S-5HIAA level, PRRT, interferon, Ki67, comorbidities (cardiovascular disease, diabetes and depression), number of regular medications, diarrhea and flushing) on HRQoL. Linear regression analysis was used to evaluate the association between HRQoL and age, gender, educational level, use of somatostatin analog, S-5HIAA concentration, PRRT, interferon, Ki67, liver metastases, comorbidities (cardiovascular disease, diabetes) and number of regular medications. Correlations were analyzed with Pearson correlation coefficient. All provided p-values are two-sided and a p-value of <0.05 was considered statistically significant. The results are given as mean and standard deviation, or as percentages.

Results

Patient characteristics

The response rate was 74 % with 134/181 patients answering the 15D and SF-36 questionnaires. Patient characteristics are given in Table 1. The mean age of the 134 respondents was 66.8±9.9 years and 55 % of them were women. Mean disease duration was 81±74 months. One-hundred and twenty-two patients (91%) had either locally advanced or metastatic disease. S-5HIAA was normal (reference range <123 nmol/l) in 69 patients (52 %). The primary tumour had been operated in 126 patients (94 %). One-hundred and six patients (79 %) received somatostatin analog therapy. Thirty-six of the 134 patients had undergone PRRT. Other medical treatments included interferon and chemotherapy (Table 1). Eighty-five patients (63 %) suffered from diarrhea (3.3±2.6 times per week) and 42 patients (31 %) from flushing (2.4±3.4 times per week).

Patients not answering the questionnaires (n=47 (26 %), age 62.7±13.4, 49% women) did not differ significantly from those returning the questionnaires regarding age or gender.

Health-related quality of life in SI-NET patients compared to the general population

15D. The mean (SD) 15D score was significantly lower in SI-NET patients compared to that of the age- and gender-standardized general population (0.864±0.105 vs. 0.905±0.028, p<0.001; Figure 1). This difference is also clinically important [10]. When comparing single dimensions, SI-NET patients had significantly impaired HRQoL on 9 of the 15 dimensions (excretion, sleeping, depression, distress, vitality, sexual activity (all p<0.001), breathing, usual activities (both p<0.01), and discomfort and symptoms (both p<0.05)). (Figure 1).

SF-36. The mean SF-36 scores in SI-NET patients were: physical functioning 78±23, role limitations due to physical health 64±41, role limitations due to emotional problems 71±38, vitality 63±21, mental health 78±17, social functioning 80±20, bodily pain 73±25 and general health 55±21. There was a significant positive correlation between the 15D score and the SF-36 dimension scores on all eight dimensions. The Pearson correlation coefficients for 15D score and SF-36 dimensions were as follows: physical functioning 0.704, role limitations due to physical health 0.637, role limitations due to emotional problems 0.571, vitality 0.744, mental health 0.665, social functioning 0.699, bodily pain 0.511 and general health 0.665, for all p<0.001.

Predictors of HRQoL in SI-NET patients

Within the patient group, only number of medications predicted impaired HRQoL in linear regression model (Table 2). HRQoL was not affected by the somatostatin analog in use (long-acting lanreotide vs long-acting octreotide, data not shown). The adjusted R square for the mean total 15D score reflecting overall HRQoL was 0.251. As fP-CgA and S-5HIAA correlated significantly, fP-CgA was left out from the analysis.

Health-Related Quality of Life in Patients with and without Impaired Excretion

Excretion, which includes both bladder and bowel function, correlated closely with self-reported diarrhea (r=-0.506, p<0.001). This dimension was compared in SI-NET patients with impairments (levels 2-5, corresponding to 15D score ≤0.8) and those with normal function (Level 1, “My bladder and bowel work

normally and without problems"). Clinical characteristics of SI-NET patients with and without impaired excretion are presented in Table 3. The mean (SD) 15D score was significantly lower in patients with impaired compared to normal excretion (0.828±0.103 vs. 0.933±0.067, p<0.001; Figure 2). The difference is also clinically important [10]. Patients with impaired excretion had a significantly higher number of defecation times per day (p<0.001) and more often suffered from diarrhea (p<0.001) compared to patients with normal excretion. Patients with impaired excretion used a significantly higher number of medications (p<0.01). Patients with normal excretion had higher Ki-67 proliferation index (p<0.05).

Patients with impaired excretion also demonstrated significantly lower dimension scores in all but one SF-36 (mental health) dimension compared to patients with normal excretion (Table 4).

Patients with self-reported diarrhea (supplementary questionnaire) had significantly lower mean (SD) 15D score (0.843±0.105 vs 0.901±0.095, p<0.01) compared to patients not reporting diarrhea, and significant impairments in 6 of the 15 single dimensions (excretion (p<0.001); breathing and discomfort and symptoms (p<0.01); mobility, mental function and vitality (p<0.05)) compared to patients not reporting diarrhea.

Discussion

In the present cross-sectional study, we found that SI-NET patients are characterized by significantly impaired HRQoL compared to a large control population of more than 1000 persons from the same catchment area despite contemporary treatments. The SI-NET patients had histologically verified disease and were treated at a single center. This enabled us to estimate the impact of a large number of factors such as disease duration, treatment modalities, comorbidities, liver metastases, Ki67 proliferation index, as well as circulating neuroendocrine tumour markers on HRQoL. Novel findings of the present study are that the dimensions of excretion, sleep, depression, distress, vitality and sexual activity all are severely impaired in patients with SI-NETs.

Some previous studies in patients with NETs of mixed origins also demonstrated impaired HRQoL [15-19]. A Norwegian study included patients with NET tumours from any part of the gastrointestinal tract (n=196) [17], a Swedish study defined the patients as having carcinoid tumour but included 36 patients only [16]. A large online anonymous survey performed in the USA reported reduced quality of life in a cohort of 663 subjects with self-reported diagnoses of carcinoid, islet cell or unknown underlying tumour [18]. The authors concluded that optimal management of NETs and carcinoid syndrome may significantly improve HRQoL among patients with NETs [18]. So far, only one previous study has reported equivalent HRQoL in the subgroup of SI-NET patients compared to a normative population [20]. However, the number of SI-NET patients in that study was small (n=44) and approximately 40 % of the patients were in remission. In the present study, 91% had local or distant metastases which may explain the lower HRQoL compared to that of the general population in our study.

Approximately 60% of SI-NET patients have metastatic disease already at diagnosis [6], most commonly including mesenteric and para-aortic lymph nodes and the liver. In patients with SI-NETs, liver and retroperitoneal metastases impair prognosis and generally introduce symptoms related to hypersecretion of serotonin and its breakdown products, as these bioactive peptides cannot be cleared by the liver. Carcinoid syndrome is found in approximately 30% of SI-NET patients at diagnosis and is characterized by diarrhea, flushing, bronchoconstriction and fatigue. Average disease duration in the present study was 81 months and a majority had metastatic disease. We therefore wanted to study the impact of circulating 5HIAA concentrations and liver metastases on HRQoL. However, neither 5HIAA concentrations nor hepatic tumour burden independently predicted HRQoL in the present study.

Diarrhea as a disease specific symptom in Si-NET was further characterized by dividing the patients in those with and those without impaired excretion score on 15D. Both mean SF-36 and 15D scores were significantly lower in patients with impaired excretion compared to patients without impaired excretion. In addition, mean 15D scores were significantly lower in patients with self-reported diarrhea compared to patients

without diarrhea. This strengthens the finding that carcinoid syndrome and, especially, diarrhea impair HRQoL in SI-NET patients.

The clinical factors studied here did not clarify the cause of diarrhea. In Si-NET patients, causes of diarrhea are multifactorial. In addition to carcinoid syndrome, HRQoL may be related to gender, extent of bowel surgery, medications or other underlying diseases [21]. To our surprise, the two groups with and without impaired excretion did not differ with regard to age, biochemical disease control, hepatic tumour burden, or treatments. Neither did the two groups differ regards resection of the primary tumour (resected in the majority of patients, 94%). Patients with impaired excretion had a higher number of medications. The underlying tumour in this group was characterized by a slightly, but significantly, lower Ki-67 proliferation index indicating that Ki-67 does not directly correlate with hormonal hypersecretion and carcinoid syndrome symptoms in SI-NETs.

The significance of the impaired excretion score and self-reported diarrhea for HRQoL in our patient group is somewhat surprising, as our patients receive contemporary therapy according to recent European treatment guidelines [22]. Altogether 79% of the patients in the present study are on somatostatin analog therapy, known not only to improve diarrhea and decrease fP-CgA and S-5HIAA concentrations, but also to have an anti-tumoural effect [12,13]. Our results imply that better treatments of diarrhea are warranted in SI-NET patients. Telotristat ethyl is a new drug for patients suffering from carcinoid syndrome, the current indication being diarrhea not adequately responding to somatostatin analog treatment [23]. Gelhorn et al and Kulke et al [24] reported that telotristat ethyl improves diarrhea and decreases bowel movement frequency in patients with carcinoid syndrome.

In addition to impaired excretion, also depression, sleep, distress, vitality and sexuality were significantly impaired. Currently, as these impairments have not been acknowledged, they render little if any attention in the clinical follow-up and treatment of SI-NET patients. The prevalence of depression and anxiety in carcinoid syndrome is approximately 50% and 35%, respectively [25-27]. A case report indicated that telotristat ethyl in combination with a low dose selective serotonin reuptake inhibitor ameliorated diarrhea and depression in somatostatin analog treatment resistant carcinoid syndrome [28]. Further studies are needed to clarify this issue. Better treatment of depression, sleeping problems and sexual health thus seem to be other important targets in the management of SI-NET patients in the future. The finding of larger number of medications as a predictor of HRQoL in the present study may reflect symptomatic treatments of diarrhea and depression or other comorbidities in this subgroup.

We also assessed the effect of PRRT, also known to improve prognosis, on HRQoL. In total, 36 of the patients had received PRRT. Even though PRRT is indicative of advanced and progressive disease, it did not predict or correlate with impaired HRQoL in our study. However, the effect of PRRT is best evaluated in a prospective setting. Earlier studies evaluating HRQoL in patients receiving PRRT demonstrated that this treatment actually improves HRQoL in NET patients [29-31] and attenuates symptoms related to the carcinoid syndrome [30-32].

We have previously used the 15D instrument when investigating HRQoL in other endocrine tumour diseases such as thyroid carcinoma [33], pituitary adenomas [34,35] and primary hyperparathyroidism [36]. Previous studies reporting impaired HRQoL in patients with NETs have utilized the SF-36 and EORTC QLQ-C30 [15-18]. In the present study, we used both the 15D and SF-36 and the results were highly correlated. An important limitation of the SF-36 is that it does not assess excretion. To the extent that the SF-36 can be regarded as a gold standard for measuring HRQoL in this patient group, the 15D therefore can be regarded as even better. The 15D is a generic, standardized and well-validated test for measuring HRQoL. Importantly, as many patients with SI-NETs suffer from symptoms that are common in the general population, such as depression and irritable bowel disease, a comparison of the findings in patients compared to a well-characterized and representative control population is essential. The 15D thus enabled us to compare HRQoL in SI-NET patients to that of a large age- and gender-standardized population.

An important limitation of the current study is that it is cross-sectional and observational. We could not adjust the 15D results of the control population for comorbidities or socioeconomic factors. Naturally, in order to evaluate the prognostic significance of our findings, a longitudinal prospective follow-up study on carefully characterized patients with SI-NETs should be performed.

In conclusion, we demonstrate that patients with SI-NETs have severely impaired HRQoL despite contemporary treatments. Current treatment options have resulted in prolonged survival rates but better treatment of depression, diarrhea, possible disturbances in sleep and sexual activity is warranted in the future.

Author contributions

HS, RR, NM and CSJ designed the study. NM, MT and IH collected the patients. NM and NK collected the clinical data. RL analyzed hepatic tumour burden. NK, RR and HS performed the statistical analyses. NK, NM and CSJ drafted and wrote the manuscript. All authors participated in writing the final version.

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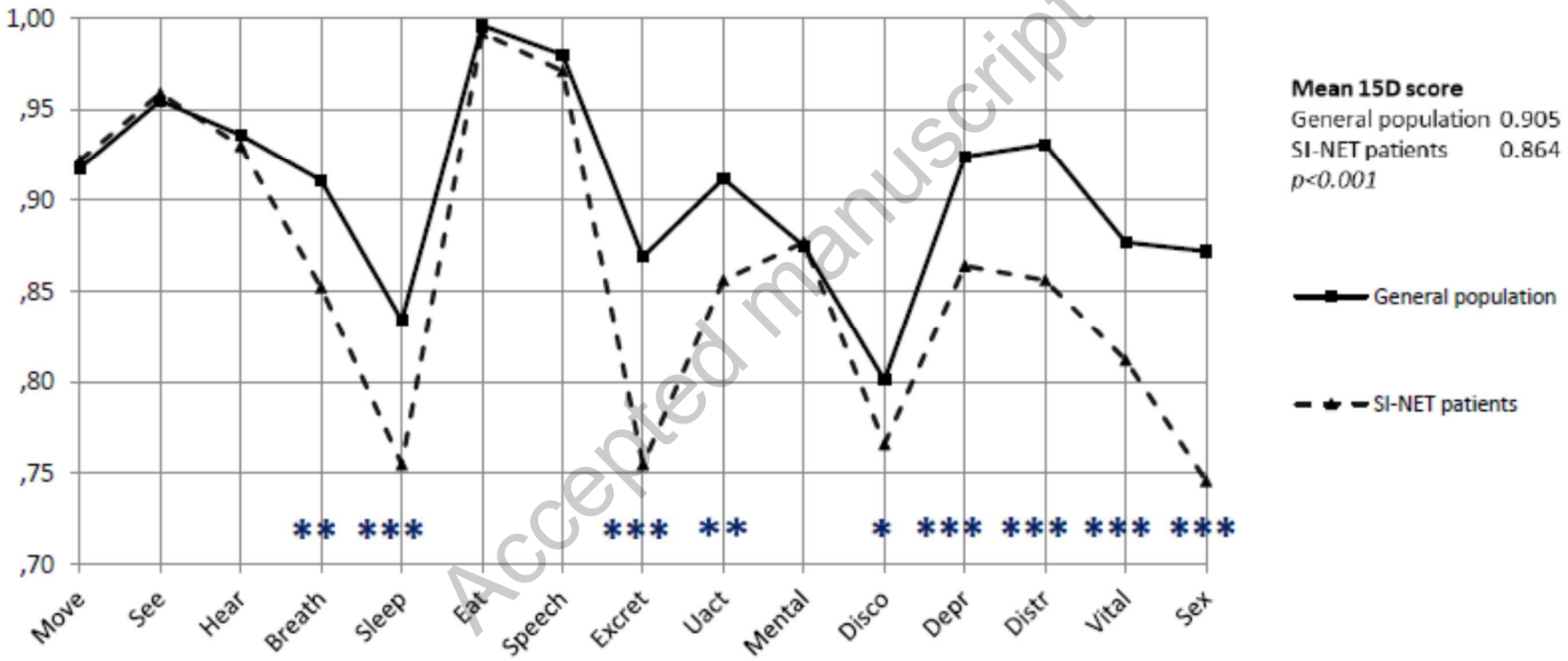
Appendix

1) The 15D Questionnaire
2) Supplementary questionnaire

Figure legends

Fig. 1. The 15D scores and profiles of SI-NET patients (n = 134) and general population controls standardized for age and gender (n = 1153). Move = mobility, See = vision, Hear = hearing, Breath = breathing, Sleep = sleeping, Eat = eating, Excret = excretion, Uact = usual activities, Mental = mental function, Disco = discomfort and symptoms, Depr = depression, Distr = distress, Vital = vitality and Sex = sexual activity. *p<0.05, **p<0.01, ***p<0.001.

Fig. 2. The 15D scores and profiles of SI-NET patients according to excretion. Move = mobility, See = vision, Hear = hearing, Breath = breathing, Sleep = sleeping, Eat = eating, Excret = excretion, Uact = usual activities, Mental = mental function, Disco = discomfort and symptoms, Depr = depression, Distr = distress, Vital = vitality and Sex = sexual activity. *p<0.05, **p<0.01, ***p<0.001.



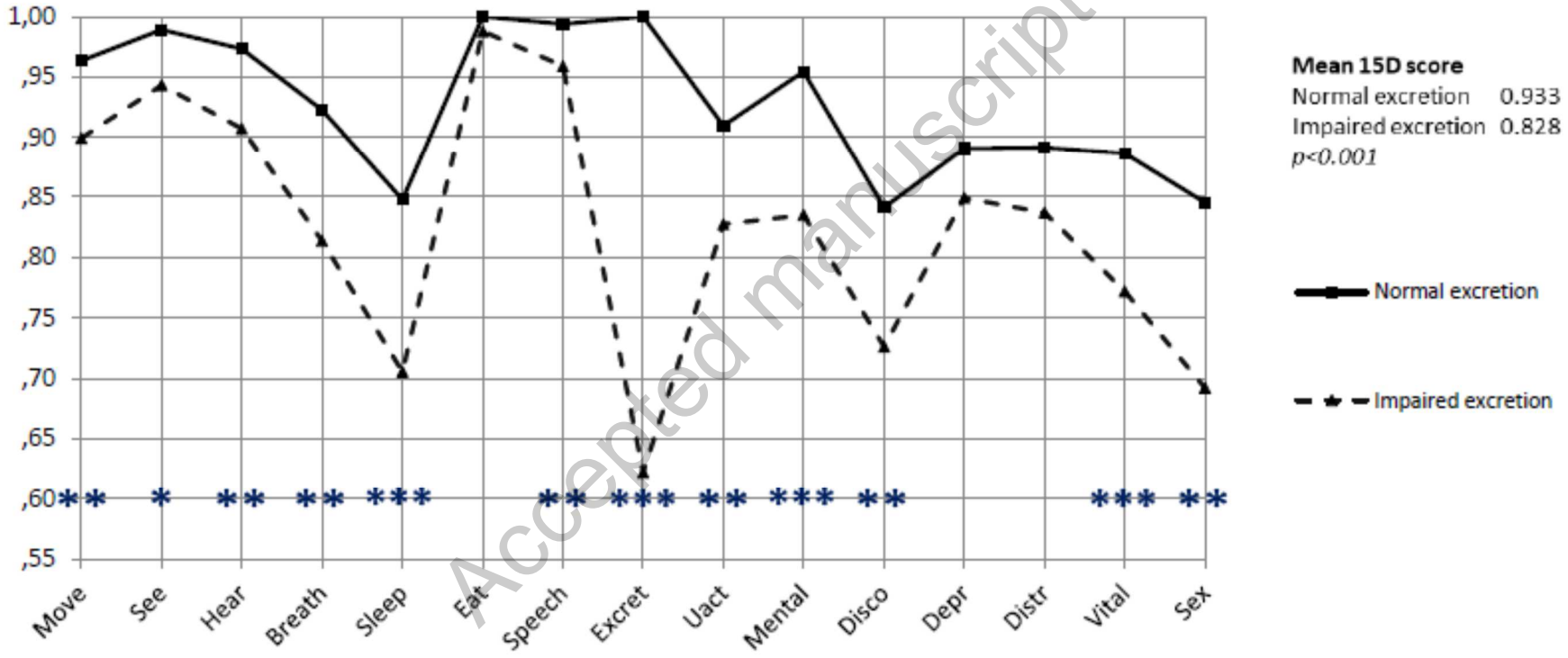


Table 1. Clinical characteristics of 134 SI-NET patients

Parameter	Mean±SD (min-max) or number (%)
Gender (female (n)/male (n))	74/60
Age (years)	66.8±9.9 (38.9-88.4)
Educational level	
Less than high school	31 (23.1 %)
High school or more	103 (76.9 %)
BMI (kg/m^2)	26.1±4.8 (17.7-42.4)
Duration of disease (months)	81±74.1 (4-468)
Ki-67 (n=133)	3.7±3.6 (0.5-15)
Grade (n=133)	
Grade 1	72 (54.1 %)
Grade 2	61 (45.9 %)
fP-CgA (nmol/l)[a]	14.6±33.8 (1.3-250)
S-5HIAA (nmol/l)[b]	344±827.9 (24-7470)
Creatinine (µmol/l)	81.7±23.3 (45-190)
Metastatic or locally advanced disease[c]	122 (91 %)
Hepatic tumour load	
0%	60 (44.8 %)
<10%	45 (33.6 %)
10-25%	14 (10.4 %)
25-50%	11 (8.2 %)
>50%	4 (3.0 %)
Flushing	42 (31 %)
frequency (times per week)	0.7±2.2
Diarrhea	85 (63 %)
frequency (times per week)	2.0±2.6
Primary tumour resected	126 (94 %)
Somatostatin analog treatment	106 (79.1 %)
Peptide receptor radionuclide therapy	36 (26.9 %)
Interferon therapy	9 (6.7 %)
Chemotherapy[d]	4 (3.0 %)

[a]Normal: <3 nmol/l

[b]Normal: <123 nmol/l

[c]At the time of the questionnaires

[d]Carboplatin, etoposide, temozolomide, capecitabine

Table 2. Linear regression analysis in SI-NET patients using the 15D total score as dependent variable

Table 3. Regression analysis in SI-NET patients using the 15D total score as dependent variable

Parameter	**Regression coefficient**	**p**
(Constant)	0.825	0.000
Age	0.001	0.327
Gender	0.027	0.124
Educational level	0.037	0.081
S-5HIAA (nmol/l)	0.000	0.504
Somatostatin analog treatment	-0.009	0.727
Peptide receptor radionuclide therapy	0.013	0.558
Interferon	0.033	0.331
Ki67	0.001	0.723
Liver metastases (yes or no)	-0.011	0.608
Cardiovascular disease	0.040	0.057
Diabetes mellitus	0.039	0.116
Number of medications	-0.019	**0.000**

Emphasis in bold denotes significant p-value <0.05.

Table 3. Clinical characteristics of patients with normal and impaired excretion (results are presented as mean±SD or number (%))

Parameter	Impaired excretion[a]	Normal excretion	p
Female (n)/male (n)	48/39	26/21	0.153
Age (yrs)	65.9±10.24	68.4±9.20	0.987
fP-CgA (nmol/l)[b]	16.3±36.5	11.4±28.5	0.423
S-5HIAA (nmol/l)[c]	394.4±951.8	252.5±528.7	0.347
Ki-67%*	3.2±3.4	4.5±3.8	**0.034**
Hepatic tumour load			
0 %	39 (44.8%)	21 (44.7%)	
<10%	28 (32.2%)	17 (36.2%)	
10-25%	8 (9.2%)	6 (12.8%)	
25-50%	9 (10.3%)	2 (4.3%)	
>50%	3 (3.4%)	1 (2.1%)	
Flushing	32 (36.8%)	10 (21.3%)	0.054
Diarrhea (times per week)	3.0±2.7	0.4±1.2	**<0.001**
Defecation (times per day)	2.7±1.6	1.7±1.0	**<0.001**
Somatostatin analog treatment	71 (81.6%)	35 (74.5%)	0.336
Cardiovascular disease	48 (55.2%)	29 (61.7%)	0.469
Diabetes	11 (12.6%)	10 (21.3%)	0.222
Depression	8 (9.2%)	4 (8.5%)	0.880
Number of medications	4.9±3.3	3.5±2.1	**0.003**

[a]Single dimension score for excretion in 15D ≤0.8

[b]Normal: <3 nmol/l

[c]Normal: <123 nmol/l

Emphasis in bold is significant p-value <0.05.

Table 4. SF-36 according to excretion

	Impaired excretion[a]	Normal excretion	p
Physical functioning	74.8±23.9	84.0±17.6	**0.012**
Role limitations due to physical health	55.6±41.8	79.9±33.6	**0.000**
Role limitations due to emotional problems	63.9±39.8	83.3±30.4	**0.002**
Vitality	58.2±20.1	72.1±20.9	**0.000**
Mental Health	76.0±15.8	81.8±17.9	0.056
Social functioning	73.5±25.5	90.7±16.6	**0.000**
Bodily pain	67.4±26.4	82.3±19.4	**0.001**
General health	49.9±19.7	64.0±19.3	**0.000**

[a]Single dimension score for excretion in 15D ≤0.8

Emphasis in bold is significant p-value <0.05.

QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes **your present health status**. Continue through all 15 questions in this manner, giving only **one** answer to each.

QUESTION 1. MOBILITY

1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION

1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING

1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION

1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION

1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS

1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY

1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

Supplementary Quality of Life Questionnaire

(To be returned with the two other questionnaires (SF-36 and 15D))

Name:_____ DOB: _____

1) Are you:
not married _____
living with someone _____
married _____
divorced _____
widowed _____

2) What is your education?
Elementary school _____
Vocational school _____
High school _____
Professional education _____
University degree _____
Other ____

3) Current medication
Brand name and dose:

_____
_____
_____
_____
_____
_____
_____
_____

4) When were you diagnosed with neuroendocrine tumor? Year_____
5) Do you have diarrhea? No_____ Yes ___ days per week
6) How frequent are your bowel movements? _____ per/day
7) Do you have flush symptoms? If yes, how often?_____
8) Do you have abdominal pain? _____No_____ Yes ___ times per/day
9) Date _____
10) You are welcome to give additional information or comments here: