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ORIGINAL SCIENTIFIC REPORT

Health-Related Quality of Life After Surgery for Small Intestinal Neuroendocrine Tumours

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Abstract

Background Overall survival for patients with small intestinal neuroendocrine tumours (siNETs) is long, even with metastatic disease, making quality of life issues relevant. The impact of surgery on quality of life is not known. We investigated determinants of health-related quality of life in patients who had undergone surgery for a siNET.

Methods Patients operated for a siNET between 1998 and 2016 at Skåne University Hospital (Lund, Sweden), who were alive in February 2017, were sent two questionnaires constructed by the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30, EORTC QLQ-GINET21). Global quality of life, physical function, disease-related worries, diarrhoea and endocrine symptoms were evaluated with linear and logistic regression in relation to patient-, tumour- and treatment-related factors. Statistical analysis was performed using STATA 11®.

Results One hundred patients (84%) completed the questionnaires. Women had worse global quality of life ($p = 0.019$), more disease-related worries ($p < 0.001$) and endocrine symptoms ($p = 0.017$) than men. Older age was associated with more disease-related worries ($p = 0.007$), but fewer endocrine symptoms ($p = 0.034$). Non-symptomatic tumour versus symptomatic tumour ($p = 0.002$), and treatment with somatostatin analogues versus no treatment ($p = 0.040$) were associated with less diarrhoea. Small versus large bowel resection was associated with better global quality of life ($p = 0.036$) and physical function ($p = 0.035$).

Conclusions Male gender, younger age, treatment with somatostatin analogues, non-symptomatic tumour, and small intestinal surgery rather than large bowel surgery were associated with better quality of life.

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Introduction

Small intestinal NETs (siNETs) are the most common gastroenteropancreatic neuroendocrine tumours (GEP-NETs) [1]. They often develop distant metastases, but then progress indolently with a favourable prognosis [2]. Several therapeutic options including surgery [3, 4], somatostatin analogues (SSAs) [5, 6], and peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-Octreotate [7, 8] can prolong survival and relieve symptoms. Given a long survival, in siNET patients the evaluation of quality of life and its determinants may be more relevant than in other cancer types with a poorer prognosis.

Health-related quality of life (HRQoL) is a multidimensional construct [9], that needs to be assessed as a patient-reported outcome. The European Organisation for Research and Treatment of Cancer (EORTC) has constructed a generic (EORTC QLQ-C30) and a specific (EORTC QLQ-GINET21) [10] questionnaire for GEP-NET patients.

Some publications [5, 6, 11–14] have reported the effects of disease-related characteristics and/or of different therapeutic strategies on HRQoL in GEP-NET patients. In a large US series, Beaumont et al. [11] demonstrated a correlation between the frequency of flushing and diarrhoea and a worse HRQoL level, but SSA use or disease spread were not significantly associated with HRQoL. The impact of medical treatment on HRQoL in GEP-NET patients was first investigated by Larsson et al. [12]. Then, Rinke et al. [5] and Caplin et al. [6] in two studies about the effect of SSAs on metastatic siNETs and GEP-NETs, respectively, demonstrated comparable levels of global QoL between the treatment and the placebo groups. Finally, after treatment with ^{177}Lu-Octreotate, an improvement in global QoL was reported by Teunissen et al. [13], while Pavel et al. [14] showed that everolimus was associated with a worsening of HRQoL for GEP-NET patients.

To the best of our knowledge, this is the first study reporting about HRQoL determinants only in surgically treated siNETs. The first aim of our study was to investigate HRQoL in patients who had already undergone a previous surgery for a siNET, and to evaluate which and how patient-related (i.e. age, gender, other diseases), disease-related (i.e. tumour grade and symptoms, tumour burden), or treatment-related (i.e. SSAs or systemic treatments, redo surgery) factors may influence the HRQoL. Another aim of the present study was to compare the HRQoL of siNET patients with the HRQoL of general and cancer populations.

Materials and methods

Study population

Patients who underwent surgery for siNETs between 1 July 1998 and 31 October 2016 at the Department of Surgery at Skåne University Hospital were identified from hospital computerised systems. All patients had a siNET confirmed by immunohistochemical analysis. Patients alive on the 1 February 2017 were sent the Swedish versions of the EORTC QLQ-C30 [15] and EORTC QLQ-GINET21 [10, 16] by regular mail together with an informed consent form. Patients were reminded once if they did not respond to the questionnaires. Patients returning completed consent forms and questionnaires constituted the study population. For these patients, we extracted data from the clinical records retrospectively using a pre-specified form and then entered it into a database. The collection of questionnaires and the evaluation of medical records were completed by May 2017.

EORTC QLQ-C30 and EORTC QLQ-GINET21

The 30-item EORTC QLQ-C30 version 3.0 (Appendix 1 of ESM) consists of functional scales, symptom scales, and a global quality of life scale. The EORTC QLQ-GINET21 version (Appendix 2 of ESM) consists of symptom, psychosocial, and functional scales. Responses to the QLQ-C30 and the QLQ-GINET21 were transformed to a 0–100 linear scale using the EORTC guidelines [17]. For the functional scales and global QoL, a high score represents a high level of functioning (i.e. better HRQoL), whereas for the symptom scales a high score indicates a high level of symptomatology (i.e. worse HRQoL).

Five major domains of HRQoL were considered as outcome variables: two functional scales (global quality of life [QL2], physical function [PF2]), one psychosocial scale (disease-related worries [DRW]) and two symptom scales (diarrhoea [DI], endocrine symptoms [ED]). In our analysis, the DRW scale was considered as a symptom scale. In a previous paper [18], global QoL, physical function, diarrhoea (all assessed by EORTC QLQ-C30) and disease-related worries (assessed by the Hospital Anxiety and Depression Scale, HADS) were found to be determinants of HRQoL in GEP-NET patients. Endocrine symptoms were the symptoms most likely to be influenced by treatment.

These HRQoL domains were evaluated in relation to 12 predictive variables: gender; age at last evaluation of medical records; other disease, or comorbidity (as reported at the last medical evaluation); type of surgery (right hemicolectomy/ileocecal resection; small intestinal

segmental resection; small intestinal/colon resection with liver resection; bypass surgery/lymph node excision); tumour grade; tumour symptoms (defined as symptoms related to a carcinoid syndrome, as reported at the last physician's evaluation); tumour burden (according to whole-body CT scan and/or ^{68}Ga-DOTATATE PET/CT performed within the last 24 months); laboratory tests (chromogranin A, urinary 5-hydroxyindoleacetic acid); SSAs therapy; systemic and locoregional tumour treatment (PRRT, chemotherapy, α-interferon, everolimus, radiofrequency ablation, trans-arterial embolisation and radioembolisation of liver metastases); symptomatic gastrointestinal and pain therapy; new biopsy and/or new surgery (performed for NET local recurrence, distant spread or carcinoid heart disease). The definition and criteria of assessment for each predictive variable are reported in Appendix 3 of ESM.

Finally, the HRQoL scores were compared with the reference values from the general population and from people affected by other cancers, as reported in the EORTC reference values manual [19].

Statistical analysis

Statistical analysis was carried out using STATA 11® (StataCorp LP, 4905 Lakeway Drive College Station, Texas 77845 USA). A Mann–Whitney *U* test and a Kruskal–Wallis test were used for univariate analysis, and then multiple linear and logistic regression analyses were performed to identify parameters with a significant influence on HRQoL. To transform the outcome continuous variables into binary ones, cut-off values for QL2, PF2 and DI were used in accordance with previous publications [20, 21], and for DRW and ED the 25th percentile was chosen as a cut-off value. We considered p values < 0.05 as statistically significant.

Ethics statement

The research ethics committee in Lund approved the present study (DNR 2015/650 and 2016/1002).

Results

Between July 1998 and October 2016, 124 patients with a siNET were operated upon in the Department of Surgery of Lund. On 1 February 2017, there were 119 survivors, with a median follow up of 47 (range 6-225) months after surgery. These patients were sent the EORTC QLQ-C30 and EORTC QLQ-GINET21 questionnaires. One hundred patients (84%) answered both questionnaires and were included in the analysis. There were 53 men and 47 women, with a median age of 71 (range 36–94) years. At the last medical evaluation, 80% of patients had no tumour symptoms, and 66 patients had distant metastases; only 41 of those had metastases at the time of initial surgery. At the time of the questionnaire, 33% of patients had mesenteric disease.

Most patients (57%) had a G1 NET. After surgery, SSAs were the therapy of choice for the majority (76%) of patients, and only 20% of patients underwent a systemic and/or a locoregional treatment (Table 1).

The mean global quality of life (QL2) score was slightly lower (66) than most of the functional scales. Disease-related worries (DRW) and diarrhoea (DI) domains had the highest (i.e. worst) mean scores (42 and 38, respectively) (Table 2). Finally, when compared to the values in the general population, as stated in the EORTC reference values manual [19], our series of siNET patients had a lower median QL2 score (67 vs. 75).

Men had better QL2 and physical function (PF2), and less DRW and endocrine symptoms (ED) than women (Table 1). In multiple linear regression analysis, QL2 ($p = 0.019$) and DRW ($p < 0.001$) were also correlated with gender (Table 3). Age seemed to be a major determinant for ED domain, with older ($\geq$ 70 years) patients having a lower ED score than the younger ones ($p = 0.034$). In linear regression, having no tumour symptoms was related to a lower DRW level ($p = 0.014$). Finally, having more than two comorbidities was significantly related to a worse PF2 score ($p = 0.048$) compared to no comorbidities.

The associations found in multiple linear regression were in part confirmed by multiple logistic regression. Particularly, in logistic regression, small intestinal segmental resection was associated both with QL2 and PF2 scores, showing an OR of 4.01 (95% CI 1.09–14.73) and of 4.67 (95% CI 1.11–19.63), respectively (Table 4). Treatment with SSAs was significantly inversely associated with a higher DI score, with an OR of 0.18 (95% CI 0.04–0.93).

Discussion

In this observational single-centre study with one hundred surgically treated siNET patients, the major determinant of quality of life was gender. Women overall reported worse quality of life, as previously demonstrated by Hjermstad et al. [20] and Michelson et al. [22] using the EORTC questionnaires in Norwegian and Swedish GEP-NET patients, respectively. Our finding is also in line with Schwartz et al. [23], who demonstrated that female GEP-NET patients had higher values on symptoms scales compared to men, and also that functional scores and global QoL markedly decreased with increasing age. In our

Table 1 Distribution of the predictor variables and results of univariate analysis (*N*, 100)

	n	QL2		PF2		DRW		DI		ED	
		Med (IQR)	*p*	Med (IQR)	*p*	Med (IQR)	*p*	Med (IQR)	*p*	Med (IQR)	*p*
Gender											
Male	53	75 (67–83)	0.002	93 (73–100)	0.019	33 (10–33)	<0.001	33 (0–33)	0.071	0 (0–0)	<0.001
Female	47	58 (38–83)		80 (67–93)		50 (33–72)		33 (0–67)		13 (0–33)	
Age											
< 70	42	67 (50–83)	0.762	93 (80–100)	0.042	38 (33–57)	0.309	33 (0–67)	0.605	10 (0–23)	0.018
≥ 70	58	67 (50–83)		80 (67–93)		33 (23–57)		33 (0–67)		0 (0–10)	
Other disease											
No	21	83 (67–83)	0.082	93 (80–100)	0.024	33 (18–57)	0.732	33 (33–67)	0.179	10 (0–17)	0.541
Single	31	67 (50–83)		93 (70–100)		33 (28–53)		33 (0–67)		0 (0–13)	
Multiple	48	67 (42–83)		77 (57–93)		33 (28–57)		33 (0–67)		0 (0–23)	
Surgery											
1	40	67 (46–83)	0.236	80 (63–93)	0.282	43 (33–62)	0.080	33 (0–67)	0.295	10 (0–23)	0.120
2	49	75 (50–83)		93 (73–100)		33 (23–67)		33 (0–67)		0 (0–10)	
3	7	83 (75–83)		100 (73–100)		33 (10–33)		33 (17–50)		0 (0–5)	
4	4	67 (63–75)		77 (63–90)		22 (5–45)		0 (0–17)		0 (0–8)	
Grade											
G1	57	67 (50–83)	0.796	80 (67–100)	0.326	33 (23–57)	0.798	33 (0–67)	0.922	0 (0–17)	0.726
G2	41	67 (50–83)		93 (77–100)		33 (23–57)		33 (0–67)		0 (0–17)	
n.a.	2										
Tumour symptoms											
No	80	67 (50–83)	0.297	93 (67–100)	0.478	33 (23–50)	0.004	33 (0–67)	<0.001	0 (0–17)	0.443
Yes	18	67 (50–83)		87 (67–93)		67 (33–100)		67 (33–100)		0 (0–23)	
n.a.	2										
Tumour burden											
NED	27	67 (46–83)	0.936	93 (67–100)	0.735	33 (20–67)	0.556	33 (0–67)	0.895	0 (0–23)	0.194
LR	7	67 (50–83)		80 (73–90)		33 (33–47)		33 (0–50)		0 (0–0)	
DM	66	67 (58–83)		80 (67–100)		33 (23–58)		33 (0–67)		0 (0–17)	
Laboratory tests											
Normal	40	75 (54–83)	0.394	93 (77–100)	0.005	33 (20–50)	0.176	33 (0–67)	0.476	0 (0–10)	0.234
Elevated	52	67 (50–83)		80 (67–93)		33 (33–67)		33 (0–67)		0 (0–23)	
n.a.	8										
SSAs therapy											
No	24	75 (50–88)	0.805	93 (70–100)	0.473	33 (18–59)	0.436	33 (0–67)	0.516	0 (0–17)	0.247
Previous	6	71 (33–100)		83 (42–100)		38 (33–47)		17 (0–67)		10 (10–23)	
Current	70	67 (50–83)		80 (67–100)		33 (23–83)		33 (0–67)		0 (0–17)	
Systemic/locoregional tumour treatment											
No	80	75 (50–83)	0.721	87 (67–100)	0.966	33 (23–57)	0.691	33 (0–67)	0.272	0 (0–17)	0.429
Previous	10	67 (58–92)		83 (73–93)		33 (10–67)		17 (0–33)		0 (0–23)	
Current	10	54 (50–83)		80 (67–100)		45 (33–67)		33 (33–67)		10 (0–43)	
Symptomatic GI/pain therapy											
No	24	75 (58–88)	0.258	93 (70–100)	0.088	33 (23–53)	0.282	33 (0–50)	0.139	0 (0–13)	0.299
Yes	76	67 (50–83)		80 (67–97)		33 (28–67)		33 (0–67)		0 (0–23)	
New biopsy/surgery											
No	86	67 (50–83)	0.554	87 (67–100)	0.952	33 (23–57)	0.606	33 (0–67)	0.514	0 (0–17)	0.940
Yes	14	63 (50–83)		83 (73–100)		43 (33–57)		33 (33–67)		0 (0–10)	

1, Right hemicolectomy/ileocecal resection; 2, small intestinal segmental resection; 3, small intestinal/colon resection with liver resection; 4, bypass surgery/lymph node excision; NED, non-evidence of disease; LR, local recurrence; DM, distant metastases; SSAs, somatostatin analogues; GI, gastrointestinal; n.a., not applicable. EORTC QLQ-C30 version 3.0: QL2, global quality of life scale; PF2, physical function; DI, diarrhoea. EORTC QLQ-GI.NET21 version: DRW, disease-related worries; ED, endocrine symptoms; Med (IQR), median (interquartile range)

Table 2 Distribution, median and mean of functional and symptoms outcome variables of EORTC QLQ-C30 version 3.0 and EORTC QLQ-GI.NET21 version

Outcome variable (missing data)	Median (IQR)	Mean (SD)
Global quality of life (1%)	67 (50–83)	66 (25)
Functional scales[a]		
Physical	87 (67–100)	79 (23)
Role	83 (50–100)	71 (33)
Cognitive (2%)	83 (67–100)	82 (23)
Emotional	75 (58–100)	73 (26)
Social	83 (67–100)	75 (30)
Social-21	77 (43–90)	68 (28)
Sexual (32%)	67 (33–100)	66 (38)
Information (2%)	100 (100–100)	91 (22)
Financial impact (1%)	0 (0–0)	10 (24)
Symptom scales[b]		
Fatigue	22 (10–56)	34 (27)
Nausea/vomiting (1%)	0 (0–17)	7 (14)
Pain	17 (0–33)	22 (28)
Dyspnoea	17 (0–33)	24 (29)
Insomnia	33 (0–33)	24 (27)
Appetite loss	0 (0–0)	11 (26)
Constipation (1%)	0 (0–0)	9 (21)
Diarrhoea	33 (0–67)	38 (34)
Endocrine (2%)	0 (0–17)	11 (18)
Gastrointestinal	23 (13–40)	27 (20)
Treatment related (33%)	10 (0–33)	18 (19)
Muscle body pain (1%)	33 (0–33)	27 (32)
Body image (1%)	0 (0–33)	16 (30)
Disease-related worries	33 (23–57)	42 (33)

IQR interquartile range, *SD* standard deviation

(%) percentage of missing data is reported in brackets

[a]Scores range from 0 to 100, with a higher score representing a higher level of function

[b]Scores range from 0 to 100, with a higher score representing a higher level of symptoms

study, the higher endocrine symptoms (ED) score reported by women ($p = 0.017$) could be related to their menopausal experience and perhaps their difficult in discriminating among different causes of "flushing" symptoms, whereas patients over 70 years old may become more used to having flushing (which may also affect QoL less than diarrhoea) and thus reported a lower ED score ($p = 0.034$), but these may be only speculative observations. Disease-related worries (DRW) in our series were associated with female gender ($p < 0.001$) and tumour symptoms ($p = 0.014$) at linear regression analysis. Patients suffering from a carcinoid syndrome may be continuously reminded of having a tumour, resulting in an

Table 3 Results of multiple linear regression analysis (*N*, 100)

	QL2		PF2		DRW		DI		ED	
	rc (95% CI)	*p*	rc (95% CI)	*p*	rc (95% CI)	*p*	rc (95% CI)	*p*	rc (95% CI)	*p*
Gender										
Male	1		1		1		1		1	
Female	− 15 (− 27/− 2)	0.019	− 10 (− 21/1)	0.078	− 25 (− 38/− 12)	<0.001	9 (− 9/26)	0.329	11 (2/19)	0.017
Age										
< 70	1		1		1		1		1	
≥ 70	− 7 (− 20/5)	0.239	− 10 (− 21/2)	0.092	− 3 (− 15/10)	0.678	9 (− 8/27)	0.291	− 10 (− 18/− 1)	0.034
Other disease										
No	1		1		1		1		1	
Single	− 11 (− 28/5)	0.168	− 7 (− 22/8)	0.339	− 4 (− 21/13)	0.656	− 11 (− 35/12)	0.331	2 (− 9/14)	0.713
Multiple	− 11 (− 26/4)	0.141	− 13 (− 27/− 0.1)	0.048	0.4 (− 15/16)	0.961	− 20 (− 41/1)	0.066	7 (− 4/17)	0.206
Surgery										
1	1		1		1		1		1	
2	− 0.6 (− 13/12)	0.917	5 (− 6/16)	0.376	− 9 (− 21/4)	0.174	2 (− 15/20)	0.808	− 1 (− 10/7)	0.75
3	14 (− 10/37)	0.256	11 (− 10/32)	0.300	14 (− 11/38)	0.263	− 10 (− 44/24)	0.547	− 9 (− 25/8)	0.295
4	− 4 (− 35/27)	0.788	− 17 (− 45/11)	0.222	3 (− 30/35)	0.873	− 27 (− 72/17)	0.226	− 7 (− 29/14)	0.492

Table 3 continued

	QL2 rc (95% CI)	*p*	PF2 rc (95% CI)	*p*	DRW rc (95% CI)	*p*	DI rc (95% CI)	*p*	ED rc (95% CI)	*p*
Grade										
G1	1		1		1		1		1	
G2	2 (− 10/13)	0.774	6 (− 4/16)	0.241	1 (− 11/13)	0.830	− 2 (− 18/14)	0.811	− 3 (− 11/5)	0.473
Tumour symptoms										
No	1		1		1		1		1	
Yes	4 (− 11/19)	0.587	− 3 (− 17/10)	0.641	20 (4/36)	0.014	− 35 (− 57/− 13)	0.002	− 1 (− 12/10)	0.832
Tumour burden										
NED	1		1		1		1		1	
LR	0.2 (− 22/23)	0.985	− 3 (− 23/18)	0.792	− 0.1 (− 23/23)	0.994	− 18 (− 50/15)	0.279	− 9 (− 25/7)	0.278
DM	8 (− 8/24)	0.318	3 (− 11/18)	0.644	− 2 (− 19/15)	0.783	− 9 (− 33/14)	0.425	− 7 (− 19/4)	0.210
Laboratory tests										
Normal	1		1		1		1		1	
Elevated	0.5 (− 13/14)	0.937	10 (− 2/23)	0.093	− 2 (− 16/12)	0.788	8 (− 12/27)	0.437	− 2 (− 12/8)	0.658
SSAs therapy										
No	1		1		1		1		1	
Previous	5 (− 18/28)	0.670	− 2 (− 22/19)	0.876	− 9 (− 33/14)	0.436	6 (− 27/39)	0.728	16 (− 1/33)	0.065
Current	8 (− 7/23)	0.313	2 (− 11/16)	0.723	12 (− 3/28)	0.121	− 8 (− 30/14)	0.481	− 2 (− 13/9)	0.715
Systemic/locoregional tumour treatment										
No	1		1		1		1		1	
Previous	7 (− 20/34)	0.606	4 (− 20/28)	0.733	5 (− 22/33)	0.695	− 24 (− 62/15)	0.223	− 9 (− 28/9)	0.324
Current	8 (− 12/29)	0.422	0.2 (− 19/19)	0.986	− 2 (− 23/20)	0.890	− 15 (− 45/15)	0.325	− 11 (− 25/4)	0.154
Symptomatic GI/pain therapy										
No	1		1		1		1		1	
Yes	6 (− 8/19)	0.402	10 (− 2/22)	0.103	5 (− 9/19)	0.497	− 3 (− 23/16)	0.719	1 (− 8/10)	0.829
New biopsy/surgery										
No	1		1		1		1		1	
Yes	− 2 (− 19/16)	0.866	3 (− 13/19)	0.731	− 11 (− 30/7)	0.211	9 (− 16/34)	0.487	7 (− 6/20)	0.276

1, Right hemicolectomy/ileocecal resection; 2, small intestinal segmental resection; 3, small intestinal/colon resection with liver resection; 4, bypass surgery/lymph node excision; NED, non-evidence of disease; LR, local recurrence; DM, distant metastases; SSAs, somatostatin analogues; GI, gastrointestinal; n.a., not applicable. EORTC QLQ-C30 version 3.0: QL2, global quality of life scale; PF2, physical function; DI, diarrhoea. EORTC QLQ-GI.NET21 version: DRW, disease-related worries; ED, endocrine symptoms; rc, regression coefficient; 95% CI, 95% confidence interval

Table 4 Results of multiple logistic regression analysis (*N*, 100)

	QL2		PF2		DRW		DI		ED	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Gender										
Male	1		1		1		1		1	
Female	2.18 (0.6–8)	0.228	1.44 (0.4–5)	0.588	0.93 (0.2–4)	0.917	0.68 (0.2–2)	0.551	0.08 (0.02–0.3)	<0.001
Age										
< 70	1		1		1		1		1	
≥70	2.53 (0.7–9)	0.147	4.06 (1–17)	0.055	13.67 (2–92)	0.007	3.22 (0.9–12)	0.082	2.05 (0.5–8)	0.307
Other disease										
No	1		1		1		1		1	
Single	0.25 (0.1–1.3)	0.096	0.16 (0.1–0.9)	0.042	0.12 (0.1–1.1)	0.062	1.57 (0.2–11)	0.643	1.55 (0.2–10)	0.651
Multiple	0.29 (0.1–1.2)	0.094	0.15 (0.1–0.8)	0.022	0.21 (0.1–2)	0.114	2.09 (0.4–11)	0.383	0.99 (0.2–5)	0.993
Surgery										
1	1		1		1		1		1	
2	4.01 (1.1–15)	0.036	4.67 (1.1–20)	0.035	1.32 (0.3–6)	0.718	2.25 (0.6–8)	0.205	1.89 (0.5–7)	0.326
3	11.47 (1.1–126)	0.046	9.06 (0.9–96)	0.067	8.99 (0.7–118)	0.095	4.92 (0.4–59)	0.209	14.98 (0.4–574)	0.146
4	21.09 (0.9–493)	0.058	23.18 (1.1–522)	0.048	1		9.75 (0.3–384)	0.224	1.85 (0.1–40)	0.694
Grade										
G1	1		1		1		1		1	
G2	2.92 (0.9–9)	0.076	1.66 (0.5–6)	0.422	1.44 (0.4–6)	0.594	0.91 (0.3–3)	0.878	2.39 (0.6–9)	0.209
Tumour symptoms										
No	1		1		1		1		1	
Yes	1.87 (0.4–9)	0.440	0.81 (0.1–5)	0.807	0.67 (0.1–4)	0.669	0.72 (0.1–4)	0.690	0.33 (0.1–1.9)	0.208
Tumour burden										
NED	1		1		1		1		1	
LR	0.75 (0.1–6)	0.792	2.66 (0.3–25)	0.394	0.69 (0.1–10)	0.786	0.85 (0.1–9)	0.895	3.55 (0.2–61)	0.383
DM	0.39 (0.1–2)	0.257	0.67 (0.1–4)	0.659	0.71 (0.1–5)	0.739	0.52 (0.1–3)	0.471	1.01 (0.1–7)	0.993
Laboratory tests										
Normal	1		1		1		1		1	
Elevated	1.37 (0.3–6)	0.667	0.65 (0.1–3)	0.595	2.85 (0.5–15)	0.212	0.43 (0.1–2)	0.257	0.77 (0.2–3)	0.729
SSAs therapy										
No	1		1		1		1		1	
Previous	6.85 (0.7–68)	0.100	0.91 (0.1–13)	0.942	0.51 (0.1–8)	0.636	0.26 (0.1–3)	0.275	0.05 (0.01–2)	0.088
Current	0.68 (0.2–3)	0.614	0.55 (0.1–3)	0.500	0.21 (0.1–2)	0.171	0.18 (0.1–0.9)	0.040	2.40 (0.4–16)	0.364
Systemic/locoregional tumour treatment										
No	1		1		1		1		1	
Previous	2.61 (0.2–38)	0.482	2.12 (0.1–36)	0.603	19.55 (0.5–723)	0.106	2.77 (0.2–42)	0.462	6.97 (0.3–175)	0.238
Current	1.16 (0.1–9)	0.892	2.14 (0.2–21)	0.511	6.99 (0.3–150)	0.214	2.33 (0.3–18)	0.418	5.51 (0.6–53)	0.139
Symptomatic GI/pain therapy										
No	1		1		1		1		1	
Yes	0.45 (0.1–2)	0.241	3.29 (0.8–14)	0.100	3.60 (0.8–16)	0.087	0.13 (0.1–0.7)	0.018	3.49 (0.6–20)	0.155
New biopsy/surgery										
No	1		1		1		1		1	
Yes	0.71 (0.1–4)	0.709	0.20 (0.1–2)	0.118	0.14 (0.1–2)	0.108	1.51 (0.3–9)	0.653	0.38 (0.1–3)	0.364

1, Right hemicolectomy/ileocecal resection; 2, small intestinal segmental resection; 3, small intestinal/colon resection with liver resection; 4, bypass surgery/lymph node excision; NED, non-evidence of disease; LR, local recurrence; DM, distant metastases; SSAs, somatostatin analogues; GI, gastrointestinal; n.a., not applicable. EORTC QLQ-C30 version 3.0: QL2, global quality of life scale; PF2, physical function; DI, diarrhoea. EORTC QLQ-GI.NET21 version: DRW, disease-related worries; ED, endocrine symptom; OR, odds ratio; 95% CI, 95% confidence interval

increased perception of disease and DRW. To explain why women have a worse perception of tumour disease could be only a matter for speculation and for future investigations, possibly related to social behaviour. A study by Derogar et al. [21] on Swedish GEP-NET patients showed worse global quality of life (QL2) and physical function (PF2) scores among the oldest, in particular for female patients. In our series, rather than with age or gender, a worse PF2 was significantly associated with having more than two comorbidities ($p = 0.048$). In a previous study on the general Swedish population [24] the number of comorbidities was shown to be the most important covariate of poor HRQoL functional scales.

Our series of siNET patients had a lower median QL2 score (67) than the general population (75), according to the EORTC reference values manual [19]. This finding is in line with Larsson et al. [25] and Fröjd et al. [18], who reported on two different series of GEP-NET patients that had a worse QL2 score when compared to the general Swedish population. In our series, the median QL2 score was comparable to all cancer patients (67) and to patients affected by a colorectal cancer (67), but it was higher than the median scores reported for oesophageal, gastric and hepato-bilio-pancreatic cancer (50, 50 and 58, respectively) [19]. When compared to colorectal cancer patients only, who are normally subjected to similar surgery, siNET patients demonstrated a higher median diarrhoea (DI) score (33 vs. 0) regardless of age or gender, as reported on GEP-NETs in Sweden by Fröjd et al. [18]. Diarrhoea in siNET patients could be related to the release of hormones rather than to the type or extent of surgical resection, and in our series a non-symptomatic tumour was significantly associated with a lower reported DI score ($p = 0.002$). Diarrhoea in these patients may also be due to the presence of mesenteric disease, but in our series patients with mesenteric disease did not show a higher DI score. Finally, if we compare the median QL2 scores in our population with all cancer patients and colorectal cancer patients, relating them to gender and age, no differences between age groups were shown, but women revealed a worse median QL2 score than men (58 vs. 75 in siNET patients, and 58 vs. 67 both in comparison with all cancer patients and with colorectal cancer patients) [19].

The majority (66%) of our patients had metastatic disease, but only 17 (26%) of them had symptoms related to a carcinoid syndrome at the time of the last medical evaluation. Usually, when a siNET spreads to the liver, the patient develops a carcinoid syndrome [26], unless well controlled by SSA therapy. In our series, most (84%) of non-symptomatic stage IV siNETs were treated with SSAs, and regression analysis showed an association between SSAs use and a lower DI score ($p = 0.040$). In a large US study on GEP-NET patients, Beaumont et al. [11] found no significant interaction between SSAs use and HRQoL, but carcinoid syndrome was significantly associated with a worse HRQoL, which was evaluated with other QoL questionnaires.

All the patients included in our study had previously been operated upon for their primary siNET and most (59%) of our patients did not have distant metastatic disease at diagnosis. Patients with siNETs and liver metastases have a 5-year survival rate of only 30% without surgical therapy [27]. Even in patients with unresectable distant metastases, the resection of the primary tumour and its lymph nodes may prolong survival [5], and it can prevent abdominal complications, such as obstruction and small bowel ischaemia [26], that are likely to affect HRQoL. However, a recent large series [28] about stage IV siNET tumours did not find any survival advantages in upfront surgery in asymptomatic patients. In our study, small intestinal segmental resection was associated with better QL2 and PF2 scores ($p = 0.036$ and $p = 0.035$, respectively), when compared to the other surgical approaches. Small bowel resection should be made if the tumour may be properly resected with this operation for HRQoL reasons. The role of resective surgery is still debated and may be further investigated in comparison with medical treatment.

Our study has some limitations due to the relatively small number of patients included and the retrospective design and data collection; moreover, HRQoL was only investigated once, but it might vary with time, and repeated measurements of HRQoL over time may give a more accurate estimate. Nevertheless, in our study many patient-, disease- and treatment-related variables were included and there was a high response rate (84%) to the questionnaires.

In conclusion, siNET patients in the present study had a lower QL2 score than the general population, but a higher score than patients with other gastrointestinal tumours. Patient-related factors, such as female gender, high age and more than two comorbidities were associated with a worse HRQoL. Somatostatin analogues use, small intestinal surgery and having no tumour symptoms were associated with a better HRQoL.

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Compliance with ethical standards

Conflict of interest Novartis Sverige AB.

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