

Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden

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Received: 23 November 2015 / Accepted: 21 March 2016 / Published online: 31 March 2016
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Abstract

Introduction Neuroendocrine tumors (NETs) are malignant solid tumors arising in hormone-secreting tissue. They have historically been very difficult to treat, and advanced NETs are considered incurable. Surgery is the only potentially curative treatment option, though research is ongoing, investigating the efficacy of targeted therapies combined with more traditional chemotherapies. Frequent bowel movements and episodes of flushing are the most common symptoms.

Methods The present study reports data from an anonymous patient survey of 663 eligible NET patients, identified with the assistance of patient advocacy groups. This study investigated the impact of treatment (surgery alone; surgery plus somatostatin analogue; other treatments) on quality of life (QOL). Finally, we investigate whether recurrent disease results in poorer QOL compared to disease treated curatively with surgery and remaining in remission.

Results and discussion Results suggest that increased frequency of bowel movements and presence of any flushing

symptoms are correlated with decreased quality of life. Treatment groups differed on most Patient Reported Outcomes Measurement Information System (PROMIS) global health and PROMIS-29 scores, including physical function, fatigue, pain, social function, and general physical and mental health, with the surgery group reporting significantly better scores than the other groups (effect size of differences ranged from 0.28 to 0.54). This may be possibly due to effective symptom control reached for these patients through surgery alone. After adjustment for carcinoid syndrome, the association with the treatment group disappeared for all domains except physical functioning. In terms of disease status, patients with recurrent disease reported poorer physical, social, and mental functions. Depression scores were similar between groups; however, patients with recurrent disease reported significantly higher anxiety compared to those with no current NET. Physical functioning was even more markedly different between groups, with recurrent NET patients reporting significantly impaired overall physical function, impaired sleep, and significant fatigue compared to those with no current NET. To our knowledge, this is the first study to comprehensively examine the effect of treatment group, disease status, and symptom burden on the quality of life in NET patients in a large sample. Limitations and future research directions are discussed.

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Keywords Bowel movement · Health-related quality of life · Neuroendocrine tumor

Introduction

Neuroendocrine tumors (NETs) are malignant solid tumors arising in hormone-secreting tissue throughout the neuroendocrine system or endocrine glands. Primary tumors can occur

in any number of organs including the lung, stomach, pancreas, small intestine, appendix, colon, and rectum. These tumors have historically been thought of as fairly rare lesions; however, their incidence has increased in the past 30 years, likely related to improvement in their classification [1]. It is now believed that these tumors are significantly more common than esophageal, gastric, pancreatic, and hepatobiliary cancers in prevalence. Average survival time depends greatly upon the primary tumor site, histology, grade, and stage and therefore is difficult to generalize across neuroendocrine tumors.

These tumors are considered to be fairly indolent in terms of their progression over time, and surgery remains the only curative treatment option. In addition, many patients present with incurable metastatic disease to the liver at the time of initial diagnosis. Unfortunately, only 10–20 % of these patients are eligible for surgical debulking [2]. A number of approaches for treating disease that has progressed to the liver have been attempted, including liver transplantation, chemoembolization, radioembolization, and thermal ablation, but these approaches are experimental and palliative, at best [3].

Streptozocin remains the only cytotoxic chemotherapy agent approved by the FDA. However, more recently, agents such as somatostatin analogs and targeted therapies including everolimus and sunitinib have been added [4]. Targeted therapies have also been combined with more traditional chemotherapy agents and have shown some promise [5].

The symptoms of neuroendocrine tumors are generally related to secretion of hormones that can result in hormonal symptoms including carcinoid syndrome. The main features of carcinoid syndrome are diarrhea and flushing; the intensity of these symptoms can vary widely. In patients with metastatic disease, given the limited treatment options available, quality of life (QOL) becomes the focus of care for patients and physicians. Several studies have measured health-related QOL in patients with NETs and have found that overall QOL is decreased compared to the general populations of the USA [6], Sweden [7], and Norway [8]. The largest of these studies [6] found that physical functioning, general health, and vitality scores were all significantly worse than the general US population. Health-related QOL burden was primarily due to the presence of carcinoid syndrome and an increased number of bowel movement or flushing episodes. In addition, scores on some subscales of the Patient Reported Outcomes Measurement Information System (PROMIS)-29 were worse in NET patients than in a mixed sample of cancer patients and survivors. These results highlight the importance of comprehensive disease management to give patients the best chance of achieving their optimal QOL. However, the question of optimal disease management as it relates to patient QOL remains unclear. This question frames the current study.

The present study presents a re-analysis of the survey data collected by Beaumont and colleagues [6]. The original article

focused on a comparison of patients with NET to the general population. In the current study, we compared PROMIS global health scores and provided greater detail on PROMIS-29 profile scores for patients based on self-reported levels of diarrhea and flushing. In addition, we investigated the impact of treatment on QOL (surgery alone, surgery plus somatostatin analogue, other treatments). Finally, we investigated whether recurrent disease results in poorer QOL compared to disease treated curatively with surgery and remaining in remission.

Methods

Invitations to complete an online anonymous survey were included in a number of publications sent by NET patient support organizations to patients and caregivers. The survey was administered via a free Web-based research management software application and consisted of a set of demographic and disease-related items, and several validated instruments including the Short Form 36 (SF-36) and the PROMIS (www.nihpromis.org) global health short form and PROMIS-29 profile. Survey completion was anonymous. Survey questions about demographic characteristics such as age, race, ethnicity, and level of education were included. Survey respondents were asked questions about their NET disease course in order to evaluate time since diagnosis, extent of disease spread, treatment history, presence of carcinoid syndrome, and frequency of bowel movements and flushing episodes (Table 1).

PROMIS is a National Institutes of Health Roadmap initiative intended to standardize PRO tools to measure common symptoms such as pain, fatigue, depression, sleep disturbance, and anxiety as well as physical, mental, and social functions. The 29-item PROMIS health profile includes four items each from seven core health domains (depression, anxiety, pain interference, physical function, fatigue, satisfaction with social role participation, and sleep disturbance). There is also an 11-point (0–10) numeric rating scale for pain intensity. Norm-based *T* scores were calculated for all domains, such that a score of 50 represents the mean of the general population (standard deviation (SD) = 10). On symptom scales (anxiety, depression, fatigue, pain, and sleep), higher scores (>50) represent worse outcomes. On function scales (physical and social role), lower scores (<50) represent worse outcomes. The PROMIS global health short form includes 10 items addressing multiple domains. It produces two summary *T* scores for Global Physical Health and Global Mental Health, with higher scores representing better health [9].

Statistical analyses

Using analysis of variance (ANOVA), we compared the groups, sorted by severity of diarrhea and flushing, on their

Table 1 Demographic and clinical characteristics of NET survey respondents ($N = 663$)

	Number	Percent
Female ^a	439	66.4
Race		
White	604	91.1
Black or African American	20	3.0
Asian	5	0.8
Other races	13	2.0
Multiple races selected	16	2.4
Race not provided	5	0.8
Hispanic ^b	19	4.2
Age, years ^c		
25–39	34	5.3
40–49	112	17.6
50–59	241	37.8
60–69	189	29.6
70–79	57	8.9
80 or older	5	0.8
Current activity level ^d		
Normal activity, without symptoms	176	26.8
Some symptoms, do not require daytime bed rest	324	49.4
Bed rest <50 % of waking day	129	19.7
Bed rest >50 % of waking day	26	4.0
Unable to get out of bed	1	0.2
Tumor type		
Carcinoid (endocrine or neuroendocrine tumor not from the pancreas)	536	80.8
Islet cell (endocrine or neuroendocrine tumor of the pancreas)	62	9.4
Do not know or not sure which type	65	9.8
Currently have NET (i.e., not surgically removed or has returned after surgery) ^e		
No	116	17.8
Yes	443	67.9
Not sure	93	14.3

Please note that portions of this were reproduced from the original article of Beaumont et al. [6]

^a $n = 2$ missing gender

^b $n = 206$ ethnicity not provided

^c $n = 25$ missing age

^d $n = 7$ missing performance status

^e $n = 11$ missing current NET status

PROMIS global and PROMIS-29 scores. Effect sizes (ESs; mean difference/pooled SD) were calculated to aid the interpretation of the magnitude of the differences. Survey participants were classified according to reported treatments into the following groups: surgery alone, surgery plus somatostatin analogue, and other treatments. ANOVA was used to compare PROMIS scores between these groups. Lastly, we compared PROMIS scores between individuals with recurrent disease and those with no current disease. No corrections were used for multiple comparisons as this study is a cross-sectional survey and intended to be hypothesis generating.

Results

A total of 663 invited NET patients participated in the survey. Their demographic and clinical characteristics are summarized in Table 1. The median time since NET diagnosis was 4 years (range = 0–34 years).

The mean PROMIS global mental health composite T score was 47.8 (SD = 9.9, range = 21–68). The mean PROMIS global physical health composite T score was 45.4 (SD = 10.3, range = 20–68). PROMIS global and PROMIS-29 scores differed between groups of patients defined by

frequency of bowel movements (all $p < 0.01$; Table 2). Patients with an average of 2–3 bowel movements per day did not differ from those with 0–1, while those with 4–7 or more bowel movements per day reported increasingly worse QOL with moderate effect sizes.

PROMIS global and PROMIS-29 scores also differed between groups of patients defined by frequency of flushing episodes (all $p < 0.001$; Table 3). Patients with even just one flushing episode per 14 days reported worse QOL than

patients with no flushing, with moderate effect sizes ranging from 0.33 to 0.50. Experiencing 2–3 flushing episodes per 14 days resulted in even worse mental and physical health with the association leveling off with additional episodes.

Most patients reported some recent or prior treatment with 50 % ($n = 322$) reporting surgery plus a somatostatin, 18 % ($n = 116$) surgery only, 30 % ($n = 194$) some other treatments or combination of treatments, and 3 % ($n = 18$) no past or current treatment at all. Thirteen patients did not provide treatment

Table 2 PROMIS global and PROMIS-29 scores by severity of diarrhea

PROMIS domain	Average number of bowel movements per day	PROMIS <i>T</i> score mean (SD)	Difference ^a	Effect size ^b	<i>p</i> value ^c
Global mental health	0–1 ($n = 141$)	49.9 (10.3)	–	–	<0.001
	2–3 ($n = 245$)	49.2 (9.4)	–0.7	–0.07	
	4–6 ($n = 134$)	46.2 (9.2)	–3.0	–0.32	
	7+ ($n = 64$)	41.7 (8.6)	–4.5	–0.50	
Global physical health	0–1 ($n = 141$)	48.7 (10.8)	–	–	<0.001
	2–3 ($n = 246$)	47.0 (9.7)	–1.7	–0.16	
	4–6 ($n = 135$)	42.8 (8.9)	–4.2	–0.45	
Anxiety	0–1 ($n = 150$)	53.2 (8.9)	–	–	0.009
	2–3 ($n = 255$)	53.5 (8.7)	0.3	0.03	
	4–6 ($n = 139$)	55.6 (9.2)	2.1	0.23	
	7+ ($n = 64$)	56.6 (8.0)	1.0	0.12	
Depression	0–1 ($n = 150$)	50.3 (8.9)	–	–	<0.001
	2–3 ($n = 255$)	50.7 (8.2)	0.4	0.05	
	4–6 ($n = 139$)	53.4 (9.6)	2.7	0.31	
	7+ ($n = 64$)	54.6 (9.4)	1.1	0.12	
Fatigue	0–1 ($n = 150$)	51.5 (11.5)	–	–	<0.001
	2–3 ($n = 254$)	53.0 (9.8)	1.5	0.14	
	4–6 ($n = 139$)	57.9 (9.3)	4.9	0.51	
	7+ ($n = 64$)	60.7 (8.9)	2.7	0.30	
Sleep disturbance	0–1 ($n = 149$)	50.2 (9.4)	–	–	<0.001
	2–3 ($n = 251$)	51.3 (9.1)	1.2	0.13	
	4–6 ($n = 139$)	53.7 (8.8)	2.3	0.26	
	7+ ($n = 64$)	58.0 (8.2)	4.4	0.51	
Pain impact	0–1 ($n = 149$)	50.0 (9.6)	–	–	<0.001
	2–3 ($n = 251$)	50.6 (8.8)	0.6	0.07	
	4–6 ($n = 139$)	54.7 (9.1)	4.1	0.46	
	7+ ($n = 64$)	57.9 (9.9)	3.1	0.33	
Physical function	0–1 ($n = 150$)	47.9 (9.2)	–	–	<0.001
	2–3 ($n = 257$)	46.2 (9.0)	–1.7	–0.19	
	4–6 ($n = 139$)	42.4 (8.7)	–3.8	–0.43	
	7+ ($n = 64$)	40.0 (9.0)	–2.5	–0.28	
Social role Satisfaction	0–1 ($n = 148$)	48.6 (10.7)	–	–	<0.001
	2–3 ($n = 251$)	48.1 (10.6)	–0.5	–0.05	
	4–6 ($n = 139$)	43.9 (10.0)	–4.2	–0.41	
	7+ ($n = 64$)	40.6 (9.0)	–3.2	–0.33	

p values less than or equal to .05 are considered significant

^a Difference between adjacent groups

^b Effect size = difference / pooled SD

^c Overall ANOVA *p* value

Table 3 PROMIS global and PROMIS-29 scores by frequency of flushing episodes

PROMIS domain	Average number of flushing episodes per 14 days	PROMIS <i>T</i> score mean (SD)	Difference ^a	Effect size ^b	<i>p</i> value ^c
Global mental health	0 (<i>n</i> = 293)	50.6 (9.1)	–	–	<0.001
	1 (<i>n</i> = 86)	47.0 (10.4)	–3.6	–0.38	
	2–3 (<i>n</i> = 113)	44.4 (9.5)	–2.6	–0.26	
	4–6 (<i>n</i> = 45)	44.2 (9.2)	–0.2	–0.02	
	7+ (<i>n</i> = 23)	43.1 (11.1)	–1.1	–0.11	
Global physical health	0 (<i>n</i> = 296)	49.0 (9.4)	–	–	<0.001
	1 (<i>n</i> = 86)	44.3 (9.5)	–4.7	–0.50	
	2–3 (<i>n</i> = 113)	40.5 (9.9)	–3.8	–0.39	
	4–6 (<i>n</i> = 45)	42.0 (10.3)	1.5	0.15	
	7+ (<i>n</i> = 23)	38.6 (10.5)	–3.4	–0.33	
Anxiety	0 (<i>n</i> = 306)	52.2 (8.2)	–	–	<0.001
	1 (<i>n</i> = 91)	55.1 (9.2)	2.9	0.34	
	2–3 (<i>n</i> = 118)	57.4 (8.7)	2.3	0.26	
	4–6 (<i>n</i> = 46)	57.2 (9.7)	–0.2	–0.02	
	7+ (<i>n</i> = 23)	57.3 (8.5)	0.1	0.01	
Depression	0 (<i>n</i> = 306)	49.3 (8.1)	–	–	<0.001
	1 (<i>n</i> = 91)	53.3 (8.9)	4.0	0.48	
	2–3 (<i>n</i> = 118)	54.6 (9.7)	1.3	0.14	
	4–6 (<i>n</i> = 46)	53.4 (9.4)	–1.2	–0.12	
	7+ (<i>n</i> = 23)	55.4 (10.3)	2.0	0.21	
Fatigue	0 (<i>n</i> = 305)	51.4 (10.1)	–	–	<0.001
	1 (<i>n</i> = 91)	55.5 (11.0)	4.1	0.40	
	2–3 (<i>n</i> = 118)	59.7 (8.7)	4.2	0.43	
	4–6 (<i>n</i> = 46)	57.3 (10.8)	–2.4	–0.26	
	7+ (<i>n</i> = 23)	61.0 (11.2)	3.7	0.34	
Sleep disturbance	0 (<i>n</i> = 303)	49.4 (8.8)	–	–	<0.001
	1 (<i>n</i> = 89)	53.5 (9.3)	4.1	0.46	
	2–3 (<i>n</i> = 118)	56.5 (8.4)	3.0	0.34	
	4–6 (<i>n</i> = 46)	55.3 (9.1)	–1.2	–0.14	
	7+ (<i>n</i> = 23)	57.8 (11.0)	2.5	0.26	
Pain impact	0 (<i>n</i> = 303)	49.4 (8.4)	–	–	<0.001
	1 (<i>n</i> = 89)	52.3 (9.8)	2.9	0.33	
	2–3 (<i>n</i> = 118)	56.6 (10.0)	4.3	0.43	
	4–6 (<i>n</i> = 46)	56.7 (9.5)	0.1	0.01	
	7+ (<i>n</i> = 23)	55.9 (10.1)	–0.8	–0.08	
Physical function	0 (<i>n</i> = 307)	47.9 (8.7)	–	–	<0.001
	1 (<i>n</i> = 91)	43.8 (9.4)	–4.1	–0.46	
	2–3 (<i>n</i> = 118)	40.9 (8.7)	–2.9	–0.32	
	4–6 (<i>n</i> = 47)	42.4 (9.2)	1.5	0.17	
	7+ (<i>n</i> = 23)	40.4 (8.1)	–2.0	–0.23	
Social role	0 (<i>n</i> = 303)	49.1 (10.5)	–	–	<0.001
	1 (<i>n</i> = 88)	45.1 (10.5)	–4.0	–0.38	
	2–3 (<i>n</i> = 118)	42.1 (10.1)	–3.0	–0.29	
	4–6 (<i>n</i> = 46)	44.1 (10.3)	2.0	0.20	
	7+ (<i>n</i> = 23)	43.4 (9.3)	–0.7	–0.07	

N = 33 “not sure” responses were excluded from the table. *p* values less than or equal to .05 are considered significant

^a Difference between adjacent groups

^b Effect size = difference / pooled SD

^c Overall ANOVA *p* value

information. Treatment groups did not differ on demographic characteristics, tumor type, or metastases. Treatment groups differed on all PROMIS global and PROMIS-29 scores except anxiety, depression, and sleep disturbance with the surgery only group reporting significantly better scores than the other groups with effect sizes of 0.28–0.54 (Table 4). Of note, only 32 % of the surgery only patients reported carcinoid syndrome, compared to 76 % of surgery plus somatostatin patients and 68 % of patients receiving other treatments. After adjustment for carcinoid syndrome, the association with treatment group disappears for all PROMIS scores except physical function.

Individuals with recurrent disease had significantly worse PROMIS global and PROMIS-29 scores compared to individuals with no current disease with effect sizes of 0.25–0.62 (Table 5).

Discussion

The results from this study suggest that patients with NETs reported that the number of bowel movements and flushing episodes significantly affected their quality of life. These results are consistent with the results from other researches [6–8]. Patients experiencing more than 4 bowel movements per day had significantly worse QOL than the other patients with NET. This may be due to the fact that these patients are continuing to attempt to function normally in terms of their social, occupational, and role functioning, but the increased demands to have a bowel movement impairs their ability to do so effectively. Patients with fewer bowel movements per day are likely able to maintain a fairly normal routine, and those with more bowel movements have perhaps accepted that they will need to make modifications to their daily routines to accommodate this disease-related symptom.

Interestingly, the actual number of flushing episodes per 14 days appeared to matter less than did the mere presence of flushing episodes. In fact, the presence of *any* flushing episodes over a 2-week period appeared to significantly and detrimentally impact quality of life. Quality of life was marginally worse in patients experiencing 2–3 flushing episodes per 14 days compared to those with just 1 flushing episode per 14 days, but then quality of life appeared to level off for any episodes greater than 3 per 14 days. These data are important, in that physicians may not be clinically concerned if patients have a small number of flushing episodes, but it is clear from this study that any flushing episodes are of significant concern from a patient perspective.

Only 32 % of patients receiving surgery only reported carcinoid syndrome compared to 76 % of patients receiving surgery plus somatostatin and 68 % of patients receiving other treatments. This could be due to the fact that patients receiving only surgery had less bulky disease or patients diagnosed at an early stage are often cured though this is unknown because data on tumor burden was not collected in the current study. It

is also possible that the use of systemic therapy is a marker of advanced disease (inoperable, relapsed, or residual disease).

In terms of disease status, patients with recurrent disease had poorer functioning (physically, mentally, and socially). Depression scores were similar between groups; however, patients with recurrent disease reported significantly higher anxiety compared to those with no current NET. Physical functioning was even more markedly different between groups, with recurrent NET patients reporting significantly impaired overall physical function, impaired sleep, and significant fatigue compared to those with no current NET, with effect sizes ranging from 0.25 to 0.62.

In the overall sample, anxiety, depression, and sleep were comparable to general population norms. This suggests that individuals with NET are able to accommodate emotionally to their symptoms over time and, as a group, may in fact be demonstrating psychosocial adjustment in ways that positively impact their quality of life.

There were some limitations in this study. Compared to the patient characteristics of NETs identified in the SEER database by Yao et al. [1], the study sample included more women (66 vs 52 %) and more Caucasian individuals (91 vs 81 %) and was younger (median age in above 50 vs 63). Also, since patients were recruited from NET support organizations, it is unknown if these patients are truly representative of all NET patients. Another limitation is the cross-sectional design, which did not allow for investigation of changes in quality of life over time and may mean that patients with especially short survival times are less likely to be included. In addition, objective clinical information, such as stage, tumor volume, and biochemical markers, was not available, and therefore, associations between these objective measures and QOL were not possible.

It should be noted that the current study utilized general HRQOL instruments in order to be able to compare NET patients to the general population. However, there are two disease-specific instruments that warrant mention. First, the European Organization for Research and Treatment of Cancer (EORTC) developed a 21-item NET-specific module [10]. This questionnaire includes three multisymptom scales: endocrine symptoms, gastrointestinal symptoms, and treatment-related adverse effects. It also includes single-item symptoms (bone/muscle pain and concern about weight loss), a social functioning scale, a disease-related worry scale, and single-item assessments of sexuality and communication. Second, the 72-item Norfolk QOL tool for patients with NETs (QOL-NET) [11] has been developed and includes domains of physical functioning, respiratory, depression, cardiovascular, gastrointestinal, flushing, and attitude.

The present research is a significant contribution to what is currently known about neuroendocrine carcinoma and quality of life. To our knowledge, this is the first study to

Table 4 PROMIS global and PROMIS-29 scores by treatment group

PROMIS domain	Treatment group	PROMIS <i>T</i> score mean (SD)	Difference	Effect size ^a	<i>p</i> value ^b
Global mental health	Surgery + somatostatin (<i>n</i> = 302)	47.6 (9.7)	S + S vs S = -2.7	-0.28	0.015 (0.247)
	Surgery only (<i>n</i> = 98)	50.3 (9.9)	S vs O = 3.6	0.36	
	Other treatments (<i>n</i> = 176)	46.7 (9.9)	S + S vs O = 0.9	0.09	
Global physical health	Surgery + somatostatin (<i>n</i> = 302)	44.8 (10.0)	S + S vs S = -4.3	-0.43	<0.001 (0.313)
	Surgery only (<i>n</i> = 99)	49.1 (10.0)	S vs O = 4.5	0.44	
	Other treatments (<i>n</i> = 177)	44.6 (10.5)	S + S vs O = 0.2	0.02	
Anxiety	Surgery + somatostatin (<i>n</i> = 309)	54.0 (8.7)	S + S vs S = 0.3	0.03	0.320 (0.212)
	Surgery only (<i>n</i> = 107)	53.7 (9.1)	S vs O = -1.4	-0.15	
	Other treatments (<i>n</i> = 185)	55.1 (9.3)	S + S vs O = -1.1	-0.12	
Depression	Surgery + somatostatin (<i>n</i> = 309)	51.6 (8.7)	S + S vs S = 0.7	0.08	0.440 (0.448)
	Surgery only (<i>n</i> = 107)	50.9 (9.3)	S vs O = -1.4	-0.15	
	Other treatments (<i>n</i> = 185)	52.3 (9.4)	S + S vs O = -0.7	-0.08	
Fatigue	Surgery + somatostatin (<i>n</i> = 308)	55.3 (10.4)	S + S vs S = 3.9	0.37	0.003 (0.558)
	Surgery only (<i>n</i> = 107)	51.4 (10.5)	S vs O = -3.7	-0.35	
	Other treatments (<i>n</i> = 185)	55.1 (10.7)	S + S vs O = 0.2	0.02	
Sleep disturbance	Surgery + somatostatin (<i>n</i> = 307)	52.5 (9.6)	S + S vs S = 0.6	0.06	0.865 (0.204)
	Surgery only (<i>n</i> = 105)	51.9 (8.7)	S vs O = -0.5	-0.06	
	Other treatments (<i>n</i> = 184)	52.4 (9.1)	S + S vs O = 0.1	0.01	
Pain impact	Surgery + somatostatin (<i>n</i> = 307)	52.9 (9.3)	S + S vs S = 3.4	0.37	0.006 (0.647)
	Surgery only (<i>n</i> = 105)	49.5 (9.1)	S vs O = -3.1	-0.32	
	Other treatments (<i>n</i> = 184)	52.6 (9.9)	S + S vs O = 0.3	0.03	
Physical function	Surgery + somatostatin (<i>n</i> = 310)	44.5 (9.0)	S + S vs S = -4.4	-0.50	<0.001 (0.025)
	Surgery only (<i>n</i> = 108)	48.9 (8.5)	S vs O = 5.0	0.54	
	Other treatments (<i>n</i> = 185)	43.9 (9.7)	S + S vs O = 0.6	0.06	
Social role	Surgery + somatostatin (<i>n</i> = 306)	45.8 (10.9)	S + S vs S = -4.4	-0.41	<0.001 (0.074)
	Surgery only (<i>n</i> = 105)	50.2 (10.7)	S vs O = 5.0	0.49	
	Other treatments (<i>n</i> = 184)	45.2 (10.0)	S + S vs O = 0.6	0.06	

N = 13 missing treatment information and *n* = 18 with no past or current treatment were excluded from the table. *p* values less than or equal to .05 are considered significant

^a Effect size = difference / pooled SD

^b Overall ANOVA *p* value; value in parentheses is the *p* value for the effect of treatment group adjusted for the presence/absence of carcinoid syndrome

comprehensively examine the effect of treatment group, disease status, and symptom burden on quality of life in a large sample of NET patients. Results suggest that increased

frequency of bowel movements and presence of any flushing symptoms are correlated with decreased quality of life. Treatment groups differed on all PROMIS global and

Table 5 PROMIS global and PROMIS-29 scores for patients with NET recurrence after surgery versus patients with no current NET

PROMIS <i>T</i> score	Recurrent disease?	PROMIS <i>T</i> score mean (SD)	Difference	Effect size ^a	<i>p</i> value ^b
Mental health composite	No (<i>n</i> = 99)	51.2 (9.6)	3.4	0.36	0.002
	Yes (<i>n</i> = 272)	47.8 (9.4)			
Physical health composite	No (<i>n</i> = 101)	50.9 (9.3)	5.9	0.62	<0.001
	Yes (<i>n</i> = 272)	45.0 (9.7)			
Anxiety	No (<i>n</i> = 107)	52.1 (8.6)	-1.7	-0.20	0.074
	Yes (<i>n</i> = 280)	53.8 (8.2)			
Depression	No (<i>n</i> = 107)	49.0 (8.7)	-2.5	-0.29	0.011
	Yes (<i>n</i> = 280)	51.5 (8.5)			
Fatigue	No (<i>n</i> = 107)	50.0 (9.9)	-5.1	-0.50	<0.001
	Yes (<i>n</i> = 279)	55.1 (10.3)			
Sleep disturbance	No (<i>n</i> = 106)	50.3 (8.8)	-2.3	-0.25	0.029
	Yes (<i>n</i> = 277)	52.6 (9.2)			
Pain impact	No (<i>n</i> = 106)	47.8 (8.6)	-4.7	-0.52	<0.001
	Yes (<i>n</i> = 277)	52.5 (9.3)			
Physical function	No (<i>n</i> = 108)	49.7 (8.2)	4.7	0.53	<0.001
	Yes (<i>n</i> = 281)	45.0 (9.2)			
Social role	No (<i>n</i> = 106)	51.5 (9.7)	5.4	0.52	<0.001
	Yes (<i>n</i> = 276)	46.1 (10.7)			

p values less than or equal to .05 are considered significant

^a Effect size = difference / pooled SD

^b *t* test *p* value

PROMIS-29 scores except anxiety, depression, and sleep disturbance with the surgery only group reporting significantly better scores than the other groups, possibly due to effective symptom control reached in these patients with surgery alone. In terms of disease status, patients with recurrent disease had poorer functioning (physically, mentally, and socially). Patients with recurrent disease reported significantly higher anxiety compared to those with no current NET. Physical functioning was even more markedly different between groups, with recurrent NET patients reporting significantly impaired overall physical function, impaired sleep, and significant fatigue compared to those with no current NET. Future research in prospective studies investigating the impact of treatment on patient-reported quality of life across the duration of the NET disease would be an important contribution to the understanding of quality of life for neuroendocrine tumor patients.

Three future research directions are suggested. First, future studies should include patient-reported measures of quality of life when examining the impact of any non-surgical, experimental treatments for NET. This is especially pertinent, given that these data suggest that there could potentially be iatrogenic complications of existing non-surgical treatments, with only a modest impact on reducing tumor burden. Second, examining the same disease-related barriers in a longitudinal sample would provide additional, and important, information on quality of life over the trajectory of illness. Finally, longitudinal studies investigating the impact of palliative measures (controlling the number of bowel movements and flushing

episodes experienced by patients) on patient-reported quality of life would be significant.

Acknowledgments The Carcinoid Cancer Awareness Network, Carcinoid Cancer Foundation, Inc., Caring for Carcinoid Foundation, and North American Neuroendocrine Tumor Society assisted in the distribution of survey invitations.

Compliance with ethical standards

Conflict of interest There are no financial disclosures to report for this manuscript. The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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