Assessment of the Association Between the Burden of Carcinoid Syndrome Symptoms and the Quality of Life Among Patients with Carcinoid Syndrome in the United States Based on the FACT-G Instrument

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Background and Objectives

- Carcinoid syndrome (CS) results secretion of bioactive amines, peptides, and polypeptides by functional neuroendocrine tumors (NETs)[1]
  - Symptoms may include diarrhea, flushing, wheezing; less frequently carcinoid heart disease, cramping, cyanosis, or peripheral edema[1]
- In one study, among US patients with NET identified between 2000 and 2011, 19% were found to have CS at diagnosis, with common subgroups such as metastatic well-differentiated small bowel NET manifesting CS in over 50% of cases[2]
- Patients with NET and CS often report reduced quality of life (QoL), particularly in areas of fatigue, general health, and physical role limitations; frequent bowel movements and flushing episodes have been shown to be significantly associated with decreased health-related QoL[3]
- The first-line systemic therapy for metastatic NETs frequently includes somatostatin analogs (SSAs) such as octreotide or lanreotide[4]
  - Octreotide, approved in 1988, is indicated for the symptomatic treatment of metastatic carcinoid tumors, targeting severe diarrhea and flushing[5]; lanreotide was approved in 2014 for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic NET to improve progression-free survival[6]
  - SSAs inhibit the secretion of gastrointestinal hormones and alleviate symptoms of CS associated with advanced NETs, such as diarrhea and flushing, and hormonal syndrome[4]
- The objective of this study was to assess the association between the burden of carcinoid syndrome symptoms (CSS) and QoL among patients with CS using the validated Functional Assessment of Cancer Therapy-General (FACT-G) instrument

Methods

Data Source

- Patients with CSS in the US were recruited via Neuroendocrine Cancer Awareness Network (NCAN), a patient advocacy group, for an online, anonymous survey between July 21 and October 31, 2016
  - Eligible patients were at least 18 years old, diagnosed with NET and CS by a physician, and received either SSA or non-SSA treatments for CSS control
  - SSAs included lanreotide, octreotide, and pasireotide. Non-SSAs included cyproheptadine, diphenoxylate-atropine, diphenhydramine, loperamide, ranitidine, and telotristate etiprate
- The survey consisted of demographic characteristics (e.g., gender, age, race), clinical characteristics (e.g., site of NET, time since NET and CS diagnoses, treatments received, CSS such as flushing episodes, bowel movements, and activity levels), and QoL questions from the FACT-G questionnaire
- Data were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA)
  - All study materials were approved by the New England Independent Review Board
  - Patients provided their informed consent prior to responding to the survey questions

Statistical Analyses

- FACT-G item scales and overall scores were calculated using the algorithm from the scoring manual[7]
  - A high score on FACT-G scales indicates a better QoL[7]
- Descriptive analyses assessing patient demographic and clinical characteristics were conducted using means and standard deviations (SDs) for continuous variables and frequencies and proportions for categorical variables
- Multivariable linear regression analyses, adjusting for demographic (sex, age, and race) and clinical characteristics (carcinoid/NET type, number or frequency of symptoms, and current activity level), were performed to assess the association between CSS and total FACT-G score, as well as FACT-G subscales (Physical Well-Being [PWB], Social Well-Being [SWB], Emotional Well-Being [EWB], and Functional Well-Being [FWB])
  - To illustrate the association between CS burden and QoL and to avoid multicollinearity due to the correlation between the CS burden questions, two multivariable models were assessed:
    - Model 1 examined CSS as defined by the total number of CSS experienced
    - Model 2 examined CSS through average number of bowel movements and flushing episodes per day
  - Statistically significant associations were noted for *P*-values < 0.05

Results

Demographic and Clinical Characteristics

- Of the 117 patients who completed the online survey, the majority were female (77%) and Caucasian (91%), with a mean age of 58.0 years **(Table 1)**
- The most common primary site of NET was ileum (47%), and the mean (SD) time since NET diagnosis to date of survey completion was 8.3 (6.0) years
- The mean time from NET diagnosis to diagnosis of CS was 1.2 years

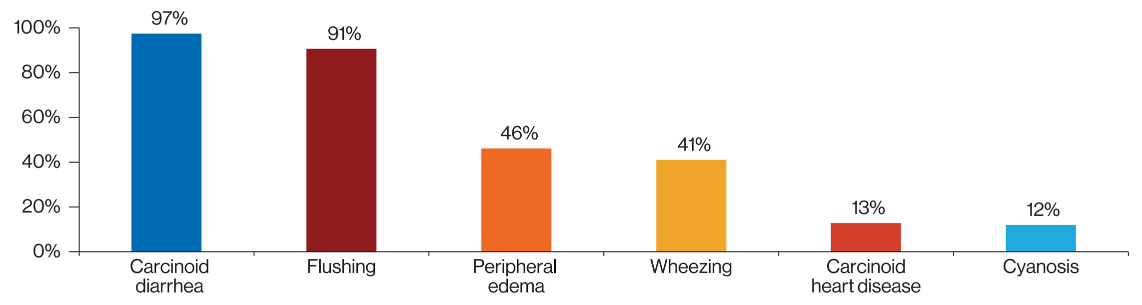
Table 1. Demographic and Clinical Characteristics

	All Patients (N=117)	
Demographic characteristics		
Age (years), mean (SD)	58.0	(9.8)
Female, N (%)	90	(77%)
Race, N (%)[1]		
Caucasian	106	(91%)
Black or African American	6	(5%)
Hispanic or Latino	5	(4%)
Asian/Pacific Islander	0	(0%)
Native American/American Indian	1	(1%)
Other	3	(3%)
Clinical characteristics		
Primary site of NET, N (%)[1]		
Ileum	55	(47%)
Appendix	12	(10%)
Lung	11	(9%)
Stomach	11	(9%)
Duodenum	10	(9%)
Colon	10	(9%)
Jejunum	6	(5%)
Rectum	0	(0%)
Other primary site[2]	30	(26%)
Time since NET diagnosis to survey completion date diagnosis (years), mean (SD)	8.3	(6.0)
Time since CS diagnosis to survey completion date (years), mean (SD)	7.1	(5.5)
Number of CSS experienced, mean (SD)	3.0	(1.13)

CS, Carcinoid Syndrome; CSS, Carcinoid Syndrome Symptoms; NET, Neuroendocrine Tumor; SD, Standard Deviation.
[1]Patients were allowed to select multiple responses.
[2]Other primary NET sites include patient-submitted responses of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.

- The most frequently reported CSS among the six different symptoms asked in the survey included carcinoid diarrhea (97%), flushing (91%), peripheral edema (46%), and wheezing (41%) **(Figure 1)**
  - 45% of the patients reported experiencing ≥4 bowel movements and 12% experienced ≥4 flushing episodes per day in the past 2 weeks **(Figure 2)**
- At the time of the survey, 85.5% had CSS without required bed rest or required bed rest during < 50% of the waking day **(Figure 3)**

Figure 1. CSS Experienced after NET Diagnosis



CS, Carcinoid Syndrome; NET, Neuroendocrine Tumor.

Treatment Characteristics

- Common NET treatments that were ever received included SSAs (94%), surgical procedures (72%), and liver-directed therapy (35%) **(Table 2)**
- For CSS treatment, the large majority of patients reported receiving SSAs in the past month (98%)
- The mean duration of CSS treatment with SSA was 6.1 (SD: 4.7, range: 0.3-21.3) years, and most patients were still receiving treatment (96%) at the time of the survey
  - 43% of patients treated with SSAs reported receiving SSA treatment for >5 years

Figure 2. Average Number of Bowel Movements and Flushing Episodes per Day in the Past 2 Weeks

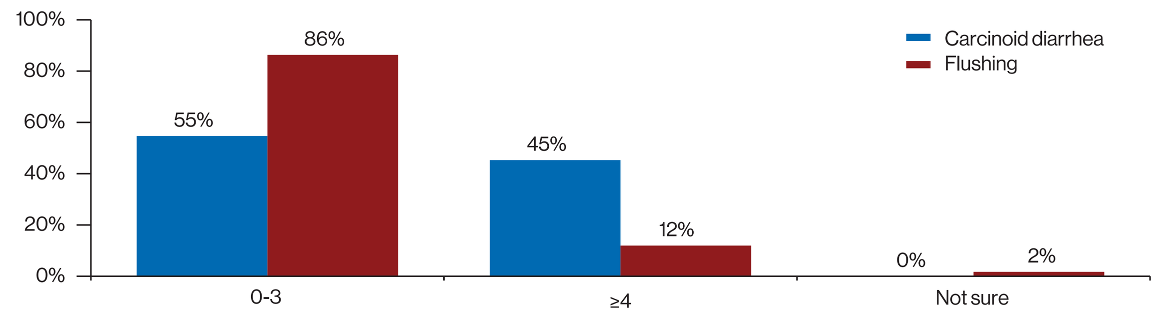


Figure 3. Current Activity Level

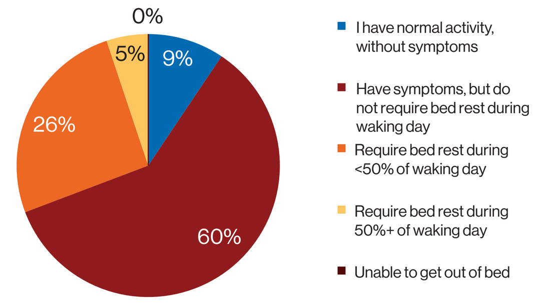


Table 2. NET and CS Treatment Characteristics

	All Patients (N=117)	
NET treatments ever received, N (%)		
SSAs	110	(94%)
Surgical procedures	84	(72%)
Liver-directed therapy	41	(35%)
Chemotherapy	24	(21%)
Targeted therapy	12	(10%)
Interferon	4	(3%)
Other[1]	11	(9%)
No treatment	0	(0%)
CSS treatments received in the past month, N (%)		
SSAs	115	(98%)
Non-SSAs	12	(10%)
Other treatment[2]	15	(13%)
No treatment	0	(0%)
Duration of CSS treatment with SSA (years)[3]		
Mean (SD)	6.1	(4.7)
Still on treatment, N (%)	111	(96%)
Discontinued, N (%)	4	(3%)

CS, Carcinoid Syndrome; CSS, Carcinoid Syndrome Symptoms; NET, Neuroendocrine Tumor; SD, Standard Deviation.
[1]Other NET treatments include: peptide-receptor radionuclide therapy (PPRT) and external beam radiation (outside of liver).
[2]Other CS treatments include patient-submitted responses of: anti-nausea medication, Cap/Tem chemotherapy, chemo embolization, Creon, Fentora for pain, Lyrica diabetic neuropathy, MIBG, narcotic analgesics, somatuline, surgery, Telestar, tincture of opium, and TSCE.
[3]Based on patients treated with SSA (N=115).

FACT-G Quality of Life Scores

Descriptive Analysis

- The mean (SD) FACT-G total score was 67.6 (20.0), which is lower than the general U.S. population score of 80.1 (18.1)[7] **(Table 3)**
- PWB, SWB, EWB, and FWB mean scores were also lower than those of the general U.S. population

Table 3. FACT-G Scores

FACT-G score, mean (SD)	Possible Range	All Patients (N=117)		General U.S. Population[7]	
FACT-G total	0 - 108	67.6	(20.0)	80.1	(18.1)
PWB	0 - 28	17.8	(6.4)	22.7	(5.4)
SWB	0 - 28	18.6	(6.5)	19.1	(6.8)
EWB	0 - 24	16.0	(4.7)	19.9	(4.8)
FWB	0 - 28	15.3	(6.7)	18.5	(6.8)

EWB, Emotional Well-Being; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; PWB, Physical Well-Being; SD, Standard Deviation; SWB, Social Well-Being; US, United States.

Multivariable regression analysis

- After adjustment, the FACT-G total score was decreased by 3.4 points (P=0.034) for each additional CSS experienced. Similarly, the PWB, SWB, EWB, and FWB scores were also reduced by 0.6 to 1.1 points **(Table 4)**
- Reduced activity levels (some symptoms but no bed rest, bed rest at <50% or ≥50% of the day, compared with normal activity) were also associated with decreases in the FACT-G total score, depending on activity level. This trend was also seen in PWB, SWB, EWB, and FWB subscales **(Table 4, Table 5)**
- ≥4 bowel movements/day was associated with a 7.1 point decrease in FACT-G total score as compared with having <4 bowel movements/day (P=0.043), and the same trend was observed in the subscales **(Table 5)**

Table 4. Multivariable Predictors of FACT-G Scores: Model 1

Total patients (N=117)	FACT-G Total			PWB			SWB			EWB			FWB		
Patient characteristics	**Est.**	**P-value**		**Est.**	**P-value**		**Est.**	**P-value**		**Est.**	**P-value**		**Est.**	**P-value**	
Male	1.9	0.637		0.8	0.490		0.2	0.916		0.1	0.932		0.8	0.533	
Age (years)	-0.1	0.558		0.0	0.710		0.0	0.791		0.0	0.833		-0.1	0.122	
Race (ref: Caucasian)															
Black or African American	4.6	0.551		1.0	0.652		1.2	0.673		0.8	0.692		1.5	0.548	
Hispanic or Latino	-0.5	0.954		2.7	0.302		-5.2	0.121		0.9	0.725		1.0	0.727	
Other	1.9	0.813		0.8	0.742		1.3	0.652		-0.4	0.847		0.2	0.935	
Clinical/symptom characteristics															
Carcinoid/NET type															
Lung	-1.2	0.839		-0.5	0.790		-0.1	0.963		0.4	0.829		-1.0	0.613	
Stomach	-6.9	0.239		-2.9	0.096		-0.1	0.973		-1.8	0.268		-2.2	0.267	
Duodenum	14.3	0.044	*	1.6	0.427		5.3	0.043	*	3.5	0.070		3.8	0.101	
Jejunum	-11.3	0.146		2.5	0.265		-6.7	0.021	*	-3.0	0.158		-4.2	0.107	
Ileum	4.3	0.295		1.4	0.247		1.6	0.283		0.6	0.596		0.7	0.615	
Appendix	-1.8	0.747		-0.3	0.833		-0.5	0.819		-0.9	0.547		-0.1	0.977	
Colon	-18.0	0.006	*	-5.2	0.007	*	-4.8	0.044	*	-1.5	0.386		-6.4	0.003	*
Other primary site[1]	1.1	0.822		-0.3	0.831		1.7	0.344		-0.9	0.490		0.6	0.696	
Number of CSS	-3.4	0.034	*	-1.0	0.032	*	-1.1	0.068		-0.7	0.116		-0.6	0.233	
Current activity level (ref: Normal activity without symptoms)															
Have some symptoms, but do not require bed rest during the waking day	-10.7	0.077		-2.3	0.204		-1.6	0.465		-1.7	0.309		-5.1	0.011	*
Require bed rest during <50% of waking day	-26.3	<0.001	*	-8.4	<0.001	*	-4.1	0.093		-3.8	0.038	*	-10.0	<0.001	*
Require bed rest during 50%+ of waking day	-42.0	<0.001	*	-14.3	<0.001	*	-2.8	0.424		-8.3	0.002	*	-16.6	<0.001	*

[1]Other primary NET sites included patient-submitted responses of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown. CSS, Carcinoid Syndrome Symptoms; Est, (Parameter) Estimate; EWB, Emotional Well-Being; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; NET, Neuroendocrine Tumor; PWB, Physical Well-Being; Ref, Reference (Group); SWB, Social Well-Being.
* P<0.05.

Table 5. Multivariable Predictors of FACT-G Scores: Model 2

Total patients (N=117)	FACT-G Total			PWB			SWB			EWB			FWB		
Patient characteristics	**Est.**	**P-value**		**Est.**	**P-value**		**Est.**	**P-value**		**Est.**	**P-value**		**Est.**	**P-value**	
Male	3.7	0.381		1.2	0.359		0.2	0.922		0.8	0.504		1.6	0.243	
Age (years)	-0.1	0.490		0.0	0.681		0.0	0.668		0.0	0.663		-0.1	0.064	
Race (ref: Caucasian)															
Black or African American	3.6	0.635		0.9	0.696		1.3	0.651		0.4	0.845		1.0	0.685	
Hispanic or Latino	2.2	0.806		3.5	0.182		-4.1	0.213		1.3	0.572		1.4	0.621	
Other	-0.1	0.993		0.3	0.912		0.6	0.838		-0.8	0.696		-0.1	0.967	
Clinical/symptom characteristics															
Carcinoid/NET type															
Lung	-1.7	0.769		-0.6	0.713		-0.3	0.895		0.3	0.865		-1.0	0.585	
Stomach	-4.4	0.454		-2.4	0.181		0.6	0.786		-1.1	0.500		-1.6	0.418	
Duodenum	11.5	0.096		0.9	0.652		4.5	0.089		2.9	0.124		3.3	0.150	
Jejunum	-6.5	0.402		3.7	0.112		-5.3	0.076		-1.9	0.365		-3.1	0.227	
Ileum	6.9	0.096		2.0	0.106		2.2	0.158		1.3	0.248		1.4	0.304	
Appendix	1.6	0.767		0.3	0.840		0.5	0.825		0.1	0.971		0.8	0.665	
Colon	-17.5	0.008	*	-5.0	0.011	*	-4.9	0.045	*	-1.4	0.428		-6.2	0.004	*
Other primary site[1]	4.6	0.325		0.7	0.632		2.8	0.118		-0.2	0.884		1.3	0.381	
Bowel movements per day in the past 2 weeks (ref: 0-3)															
4+	-7.1	0.043	*	-1.4	0.178		-1.3	0.319		-2.1	0.024	*	-2.2	0.051	
Flushing episodes per day in the past 2 weeks (ref: 0-3)															
4+	-9.0	0.079		-2.3	0.134		-0.7	0.734		-2.8	0.044	*	-3.3	0.053	
Not sure	-17.3	0.172		-2.7	0.482		-6.3	0.192		-5.1	0.138		-3.3	0.427	
Current activity level (ref: Normal activity without symptoms)															
Have some symptoms, but do not require bed rest during the waking day	-8.3	0.179		-1.7	0.351		-1.7	0.472		-0.9	0.603		-4.1	0.048	*
Require bed rest during <50% of waking day	-25.4	<0.001	*	-8.4	<0.001	*	-4.6	0.068		-3.3	0.071		-9.2	<0.001	*
Require bed rest during 50%+ of waking day	-35.5	<0.001	*	-13.0	<0.001	*	-2.2	0.566		-6.2	0.023	*	-14.2	<0.001	*

[1]Other primary NET sites included patient-submitted responses of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown. Est, (Parameter) Estimate; EWB, Emotional Well-Being; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; NET, Neuroendocrine Tumor; PWB, Physical Well-Being; Ref, Reference (Group); SWB, Social Well-Being.
* P<0.05.

Limitations

- Recruitment was conducted primarily through NCAN, which may have resulted in a potentially biased sample not fully representative of the heterogeneous NET patient population. Patients may be highly engaged and motivated care seekers
- All data were self-reported and could have been subject to recall bias
- Results are based on QoL assessment at single time point
- This study did not attempt to assess the QoL associated with any type of treatment. This would require controlling on treatment type and duration of each treatment received, which was not performed in the present analysis, but is considered in another analysis

Conclusions

- This study suggests that CSS burden as captured by the number of CSS experienced as well as frequency of flushing and bowel movements and impaired activity levels are associated with lower QoL, as demonstrated by FACT-G. Additionally, this research indicates that benefits gained by controlling CSS may lead to improvements in QoL. Future studies are needed to assess the possible impact of optimal management of CS symptoms on QoL
- Patients with CSS reported lower FACT-G scores compared with the general population
- The results contribute additional findings on the impact of CSS burden on QoL using FACT-G

References

1. Creutzfeldt W. *World J Surg* 1996; 20(2):126-131.
2. Halperin D et al. *Lancet Oncol* 2017 Apr;18(4):525-534.7.
3. Beaumont J et al. *Pancreas* 2012 Apr;41(3):461-466.
4. Kulke MH. *Journal of the National Comprehensive Cancer Network* 2016 Mar;14(3):241-2.
5. Sandostatin LAR Prescribing Information. Available at https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/sandostatin_lar.pdf.
6. SOMATULINE DEPOT Prescribing Information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022074s011lbl.pdf.
7. Webster K et al. *Health and quality of life outcomes* 2003 Dec;1(1):79.

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