Ann Surg Oncol (2019) 26:2711–2721
https://doi.org/10.1245/s10434-019-07441-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Symptom Burden at the End of Life for Neuroendocrine Tumors: An Analysis of 2579 Prospectively Collected Patient-Reported Outcomes

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ABSTRACT

Background. Given a slow course of disease, end-of-life issues are understudied in neuroendocrine tumors (NETs). To date, there are no data regarding symptoms at the end of life. This study examined symptom trajectories and factors associated with high symptom burden in NETs at the end of life.

Methods. We conducted a retrospective cohort study of NET patients diagnosed from 2004 to 2015 and who died between 2007 and 2016, in Ontario, Canada. Prospectively collected patient-reported Edmonton Symptom Assessment System scores were linked to administrative healthcare datasets. Moderate-to-severe symptom scores ($\geq$ 4 out of 10) in the 6 months before death were analyzed, with multivariable modified Poisson regression identifying factors associated with moderate-to-severe symptoms scores.

Results. Among 677 NET decedents, 2579 symptom assessments were recorded. Overall, moderate-to-severe scores were most common for tiredness (86%), wellbeing (81%), lack of appetite (75%), and drowsiness (68%), with these proportions increasing as death approached. For symptoms of lack of appetite, drowsiness, and shortness of breath, the increase was steepest in the 8 weeks before death. On multivariable analyses, the risk of moderate-to-severe symptoms was significantly higher in the last 2 months before death and for patients with shorter survival ($<$ 6 months). Women had higher risks of anxiety, nausea, and pain.

Conclusion. A high prevalence of moderate-to-severe symptoms was observed for NETs at the end of life, not previously described. The proportion of moderate-to-severe symptoms increases steeply as death nears, highlighting an opportunity for improved management. Combined with identified factors associated with moderate-to-severe symptoms, this information is important to improve patient-centred and personalized supportive care for NETs at the end of life.

With increased incidence observed worldwide, neuroendocrine tumors (NETs) are no longer considered a rare malignancy; their prevalence now surpasses that of gastric,

Part of this work was accepted for presentation at the Annual Cancer Symposium of the Society of Surgical Oncology held in March 2018 in San Diego, CA, USA, and presented at the American Society of Clinical Oncology Gastrointestinal Symposium (ASCO GI) held in January 2018 in San Francisco, CA, USA.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07441-5) contains supplementary material, which is available to authorized users.

First Received: 6 February 2019;
Published Online: 30 May 2019

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esophageal and pancreatic cancers combined.[1,2] Due to the lack of awareness in the public and medical community, as well as non-standardized care pathways, patients have expressed difficulty finding support in their cancer journey[3,4] The unique hormonal secretion patterns of NETs combined with a prolonged natural history can lead to debilitating systemic symptoms and quality of life.[5]

The data on NET patients' experience, symptom burden, and quality of life have focused on the initial period of care, preceding or immediately following diagnosis.[3,4,6–11] Quality of life measures and symptom assessments have also been included in randomized controlled trials of new therapies;[12–16] however, no information is currently available regarding patient experience and symptoms at the end of life, when symptom control is critical and may be particularly burdensome.[17] Examining symptom trajectories over time is essential for improving interventions to control symptoms and better support patients.

This study sought to examine symptom trajectories and factors associated with symptom severity for NETs at the end of life using prospectively collected patient-reported outcomes (PROs).

METHODS

Study Design

We conducted a retrospective observational cohort study using prospectively collected population-level PRO data linked to administrative health databases at the ICES using unique encoded identifiers. The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board and was conducted and reported following the RECORD statement.[18]

Data Sources

The Ontario Cancer Registry (OCR) includes approximately 95% of patients diagnosed with cancer in Ontario since 1964.[20,21] The reliability of its data has previously been ascertained and reported.[22–24] The Registered Persons Database (RPDB) contains vital status and demographic data on all individuals covered under the Ontario Health Insurance Plan (OHIP).[19] Information regarding health services provided is included in the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), the National Ambulatory Care Reporting System, and the OHIP Claims Database.[26]

We used Edmonton Symptom Assessment System (ESAS) scores reported by patients during outpatient visits to cancer clinics.[20,21] Monitoring of ESAS scores was initiated by Cancer Care Ontario (CCO) in 2007. Considering the prolonged survival of patients with NETs, we included NET diagnoses starting in 2004 to capture patients with earlier diagnoses who may have died after the implementation of the symptom management program.[1]

Study Population and Cohort

Under the Canada Health Act, the 13.5 million residents of Ontario benefit from universally accessible and publicly funded health care through the OHIP.[22]

Patients in the OCR with a diagnosis of NET were identified using International Classification of Diseases for Oncology, Third Revision (ICD-O-3) codes (electronic supplementary Table 1). Patients $\geq$ 18 years of age diagnosed between 2004 and 2015, who died between 1 June 2007 and 31 December 2016, and who reported at least one ESAS score during the 6 months prior to death, were included in our study. Patients were excluded if they had another cancer diagnosis prior or subsequent to the NET diagnosis, or had a date of death recorded prior to diagnosis. The characteristics of eligible NET patients who did and did not receive ESAS screening were compared to appreciate the generalizability of the findings (electronic supplementary Table 2).

Outcomes

Patient-reported moderate-to-severe symptom severity was defined using the ESAS score. The ESAS is a PRO Tool assessing the severity of nine common cancer-associated symptoms: pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and overall wellbeing. Its validity and reliability have been demonstrated in cancer populations.[23,24] ESAS scores use a numeric scale from 0 (no symptoms) to 10 (worst possible symptoms) (electronic supplementary Fig. 1).

We defined moderate-to-severe symptoms as a score $\geq$ 4 for a particular symptom.[20,25] This method has been previously shown to identify clinically significant symptom burden.[26] To determine the timing of ESAS scores, date of death was defined as time zero, and 2-week intervals were defined counting backward. If more than one symptom score was reported in a given timeframe, the highest score was retained.

Covariates

Urban living was determined using the postal code of residence in an urban area based on the national census definition of a community of more than 10,000 people,[27] while socioeconomic status (SES) was assessed using an ecologic measure of income quintile based on the median income of a patient's postal code of residence using

national census data.[28] Baseline comorbidity burden was measured using the Johns Hopkins Adjusted Clinical Groups System score based on health services use with a 24-month look-back window prior to the date of death.[29,30] The 32 aggregated diagnosis groups (ADGs) were summed to create a total score, then dichotomized with a cut-off of 10 for high comorbidity burden.[30]

NETs were subdivided, according to the primary tumor site, into bronchopulmonary, gastroenteric, pancreatic, and others, using ICD-O-3 topography codes. Metastatic disease at the time of death was defined using ICD-O-3 codes (electronic supplementary Table 1). Palliative care assessment and therapies were captured using physicians' claims and the ALR, including surgery, liver embolization, systemic therapy, and radiation therapy.

Statistical Analysis

Categorical variables were reported as absolute number (*n*) and proportion (%). The characteristics of patients who recorded at least one ESAS score in the last 6 months of life were compared with those who did not, using Chi square testing, to appreciate the generalizability of the findings.

ESAS scores were reported as the proportion of moderate-to-severe scores for each symptom in each 2-week interval prior to death. The proportion of patients with moderate-to-severe scores was plotted over the last 6 months prior to death.

The symptoms screening program in Ontario was gradually implemented from 2007 onwards. We planned a sensitivity analysis to test the robustness of the results to the decision to include patients who died at the beginning of the program. This analysis was restricted to a cohort of patients with a date of death during the period with higher ESAS uptake screening, when the program was better established (2010–2016).

Possible predictors of moderate-to-severe scores were examined, i.e. age (categorical), sex, SES, urban living, comorbidity burden, time period of death (before vs. after 2012), primary tumor site, metastatic status (metastases at the time of death, or none), therapy received over the course of NETs (chemotherapy, local invasive therapy—including surgery and liver embolization, or radiotherapy, over the course of disease), length of survival since diagnosis (categorical), and proximity to death (number of months prior to the date of death in which the ESAS score was recorded—categorical). These factors were selected a priori as potentially associated with symptoms based on clinical relevance (markers of complexity of NETs) and existing literature (known relationship with NET care and experience). Univariate and multivariate modified Poisson regression models were created, and generalized estimating equations with exchangeable correlation structures were

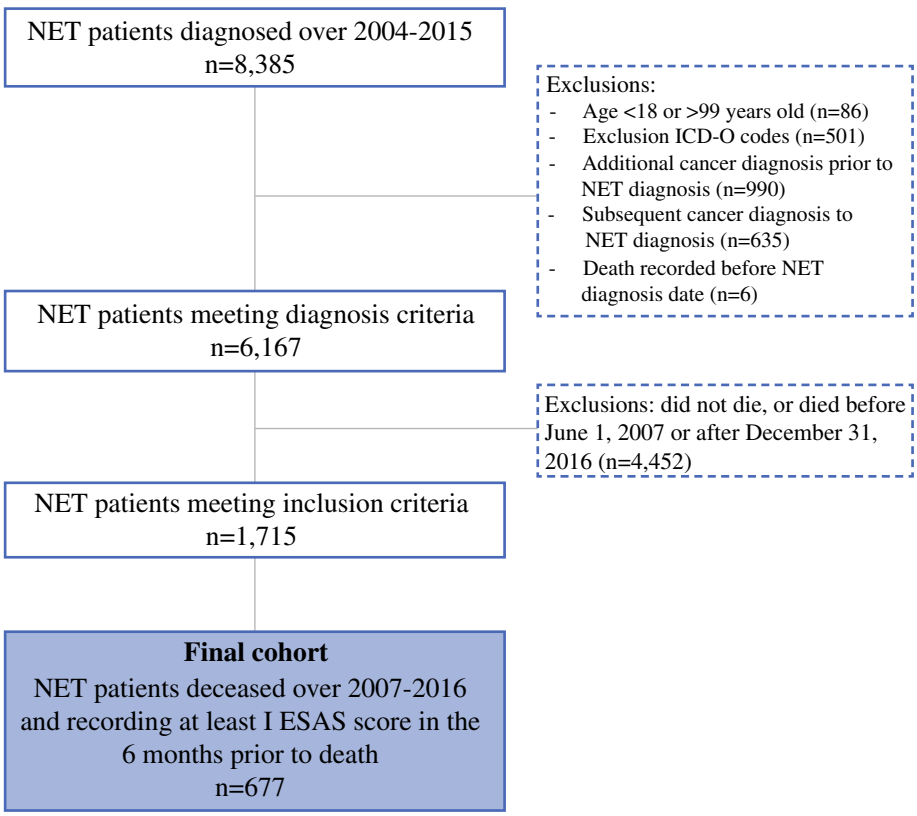


FIG. 1 Cohort selection process. *NET* neuroendocrine tumor, *ICD-O* International Classification of Diseases for Oncology, *ESAS* Edmonton Symptom Assessment System

used to account for clustering of repeated measures within patients.[31] The results are reported as relative risk (RR) with 95% confidence interval (CI) for each ESAS symptom score.

Analyses were performed using SAS 7.1 (SAS Institute, Cary, NC, USA), and results were considered statistically significant at $p \leq 0.05$.

RESULTS

Study Population

A total of 2579 unique ESAS assessments from 677 NET decedents who recorded at least one ESAS score in the 6 months before death were included (Fig. 1). A comparison of patients who did and did not record ESAS scores at the end of life is presented in electronic supplementary Table 2. On average, patients recorded 3.8 scores (standard deviation 3.5) over the 6 months before death. Patient characteristics are detailed in Table 1. Over the last 6 months before death, few patients received surgery for primary (3.7%) or liver (2.1%) resection, or liver embolization (4.4%), and the most frequent therapies were systemic therapy for 48.2% of patients and radiation therapy for 34.3% of patients. Only 2.1% of patients received palliative care assessment at the end of life.

Symptom Patterns at the End of Life

The proportion of patients reporting at least one moderate-to-severe symptom score at the end of life is summarized in Fig. 2. The symptoms most commonly reported as elevated in the last 6 months of life for all NETs were tiredness (86%), followed by overall wellbeing (81%), lack of appetite (75%), and drowsiness (68%). Similar distributions were observed when stratifying by primary tumor site (Fig. 2).

The proportion of patients reporting moderate-to-severe symptoms in the last 6 months of life is described in Fig. 3. This proportion increased progressively closer to death for all symptoms, rising from 56.8% to 83.9% for tiredness, 50.5% to 73.1% for wellbeing, 40.9% to 80.6% for lack of appetite, and 41.5% to 68.8% for drowsiness. The increase was steepest in the 8 weeks prior to death for lack of appetite, drowsiness, and shortness of breath. Stratifying results by primary tumor site did not change these observations (Fig. 4, electronic supplementary Fig. 1), except for higher proportion of moderate-to-severe shortness of breath in bronchopulmonary NETs.

The results were not altered by the sensitivity analysis restricted to patients with a date of death between 2010 and 2016 (electronic supplementary Fig. 2).

TABLE 1 Characteristics of patients diagnosed with NETs and recording at least one ESAS assessment in the last 6 months of life

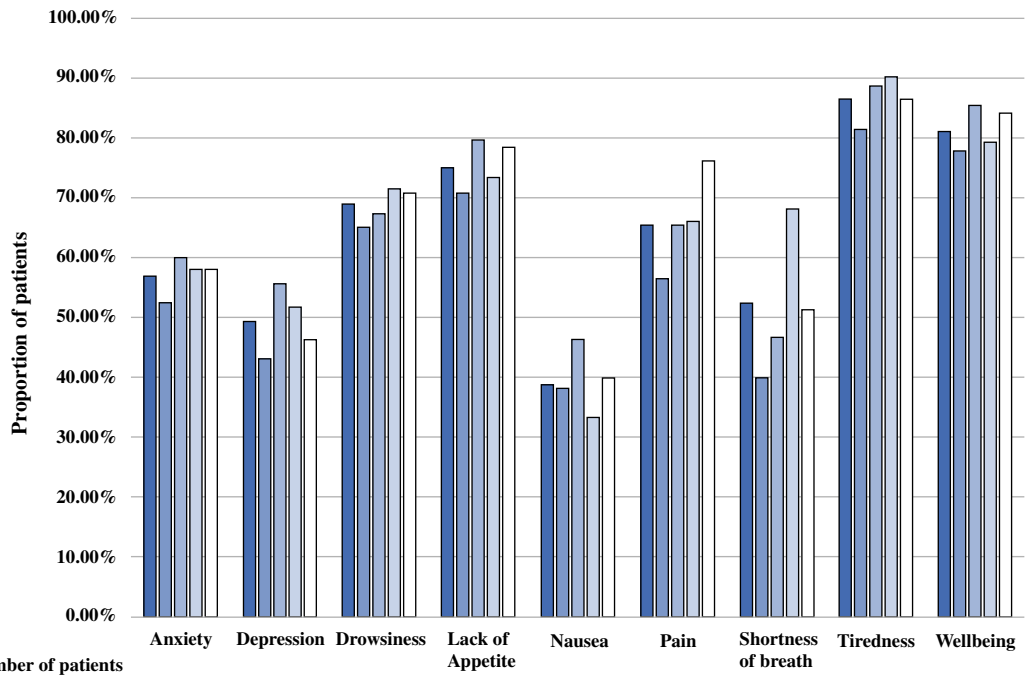
Variables	NET patients [*N* = 677]
Age categories, years	
18–39	18 (2.7)
40–59	178 (26.3)
60–79	405 (59.8)
80–99	76 (11.2)
Female sex	318 (47.0)
Year of death	
2007	13 (1.9)
2008	33 (4.9)
2009	50 (7.4)
2010	57 (8.4)
2011	72 (10.6)
2012	83 (12.3)
2013	71 (10.5)
2014	106 (15.7)
2015	90 (13.3)
2016	102 (15.1)
Urban residence	617 (91.1)
Socioeconomic status quintile	
First (lowest)	114 (16.8)
Second	139 (20.5)
Third	120 (17.7)
Fourth	158 (23.3)
Fifth (highest)	143 (21.1)
High comorbidity burden (ACG $\geq$ 10)	446 (65.9)
NET site	
Gastroenteric	179 (26.4)
Pancreatic	136 (20.1)
Bronchopulmonary	219 (32.3)
Others	143 (21.1)
Metastases at the time of death	508 (75.0)

Data are expressed as *n* (%)

NETs neuroendocrine tumors, *ACG* Aggregated Clinical Groups, *ESAS* Edmonton Symptom Assessment System

Factors Associated with Elevated Symptom Burden at the End of Life

The risks of reporting moderate-to-severe symptom scores varied based on disease characteristics (Tables 2, 3). Primary NET site was not associated with risk of reporting moderate-to-severe symptoms, excepted for lower risk of shortness of breath for all sites compared with bronchopulmonary, and lower risk of pain for gastroenteric primary NETs (RR 0.82, 95% CI 0.68–0.98). Metastatic status at the time of death was not associated with symptom



Absolute number of patients

	All (n=677)	384	331	464	506	562	443	756	585	548
	Gastro-enteric (n=179)	93	77	116	126	69	101	71	146	139
	Pancreatic (n=136)	81	75	91	108	63	89	63	120	116
	Broncho-palmonary (n=219)	127	113	156	160	73	144	149	1979	173
	Others (n=143)	83	66	101	112	57	109	73	123	120

FIG. 2 Proportion of patients with NETs reporting at least one ESAS score ≥ 4 (moderate-to-severe) for each symptom at any time during the last 6 months of life, for all NETs and stratified by primary tumor site ($n = 677$). *NETs* neuroendocrine tumors, *ESAS* Edmonton Symptom Assessment System

severity, except for lower risk of shortness of breath (RR 0.81, 95% CI 0.68–0.86).

The risk of reporting moderate-to-severe symptom scores for anxiety, depression, drowsiness, lack of appetite, nausea, pain, shortness of breath, tiredness, and overall wellbeing increased with each month closer to death for the last 3 months, and in the fourth and last month prior to death for depression. Patients with shorter survival (0–6 months from diagnosis) had a higher risk of reporting moderate-to-severe anxiety (RR 1.22, 95% CI 1.01–1.47) and lack of appetite (RR 1.19, 95% CI 1.03–1.37) compared with patients who survived over 24 months.

With regard to patient factors, age was not associated with risk of moderate-to-severe symptom scores. The main independent association identified was higher risk of reporting moderate-to-severe anxiety (RR 1.30, 95% CI 1.12–1.50), nausea (RR 1.30, 95% CI 1.06–1.61), and pain (RR 1.22, 95% CI 1.08–1.38) for women compared with men.

DISCUSSION

This is first ever study of symptom burden at the end of life for NETs. Cancer care requires longitudinal management of symptoms across the disease course, especially at the end of life when symptoms may be particularly burdensome.[32] This analysis provides a longitudinal view of symptom trajectories in the last 6 months of life using prospectively collected, validated PRO outcomes. It uncovers high needs for supportive care in the NET population at the end of life, with a steep increase as death nears.

Previous studies of NET patients' experience focused on the peri-diagnostic and treatment initiation (initial or for progression) periods of care.[3,4,6–11] These studies relied on volunteered patient surveys and quality-of-life questionnaires, and were cross-sectional in nature.[3,9] The current analysis adds to the existing literature by providing the first assessment of symptom burden for NET patients at the end of life, based on prospectively administered, validated, and reliable PRO measures.[23,24] This period of the NET cancer journey had not been studied before.

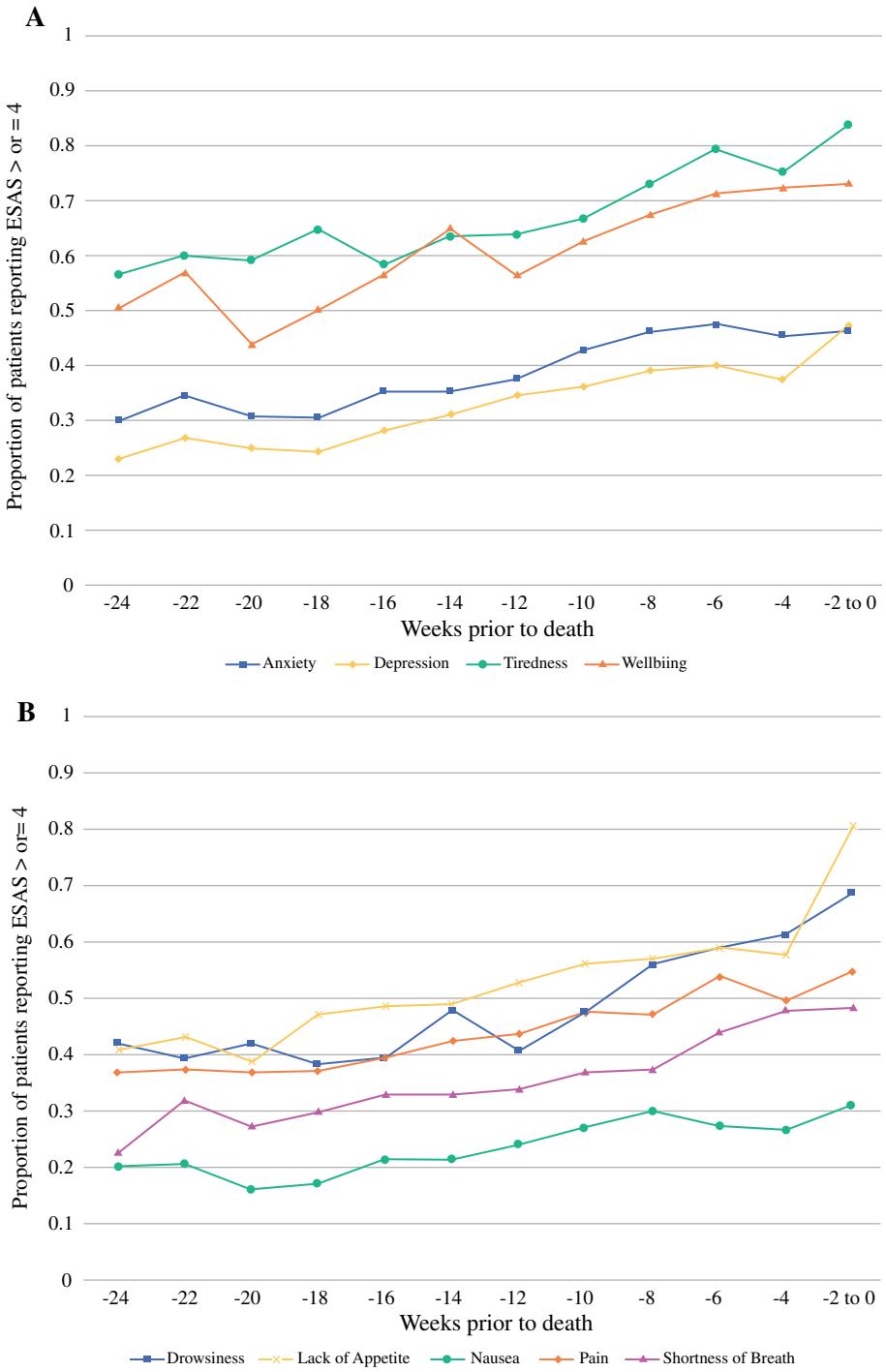


FIG. 3 Proportion of patients with NETs reporting at least one moderate-to-severe (≥ 4) ESAS score in the last 6 months of life, for each symptom, i.e. **a** anxiety, depression, tiredness, and overall wellbeing, and **b** drowsiness, lack of appetite, nausea, pain, and shortness of breath). Trend lines do not represent continuous data but are included to facilitate the visualization of trends over time by symptom. *NETs* neuroendocrine tumors, *ESAS* Edmonton Symptom Assessment System

Even though a high and progressively increasing symptom burden at the end of life can appear intuitive, this description bears important implications, and will contribute to improving patients' distress. Tiredness, lack of appetite, depression, and pain are all predictors of the desire for hastened death, which indicates underlying distress and affects up to one of five cancer patients.[33,34] Furthermore, it will improve the medical community's knowledge regarding end-of-life care for NETs. Decision making at the end of life requires proactive considerations of quality of life and symptom control. The data presented herein are important in raising awareness and supporting better integration of patient-centred care at the end of life.

The preceding cancer journey of NETs and hormonal secretion patterns can result in unique symptoms close to death.[1,2,35] In addition, NET patients have expressed

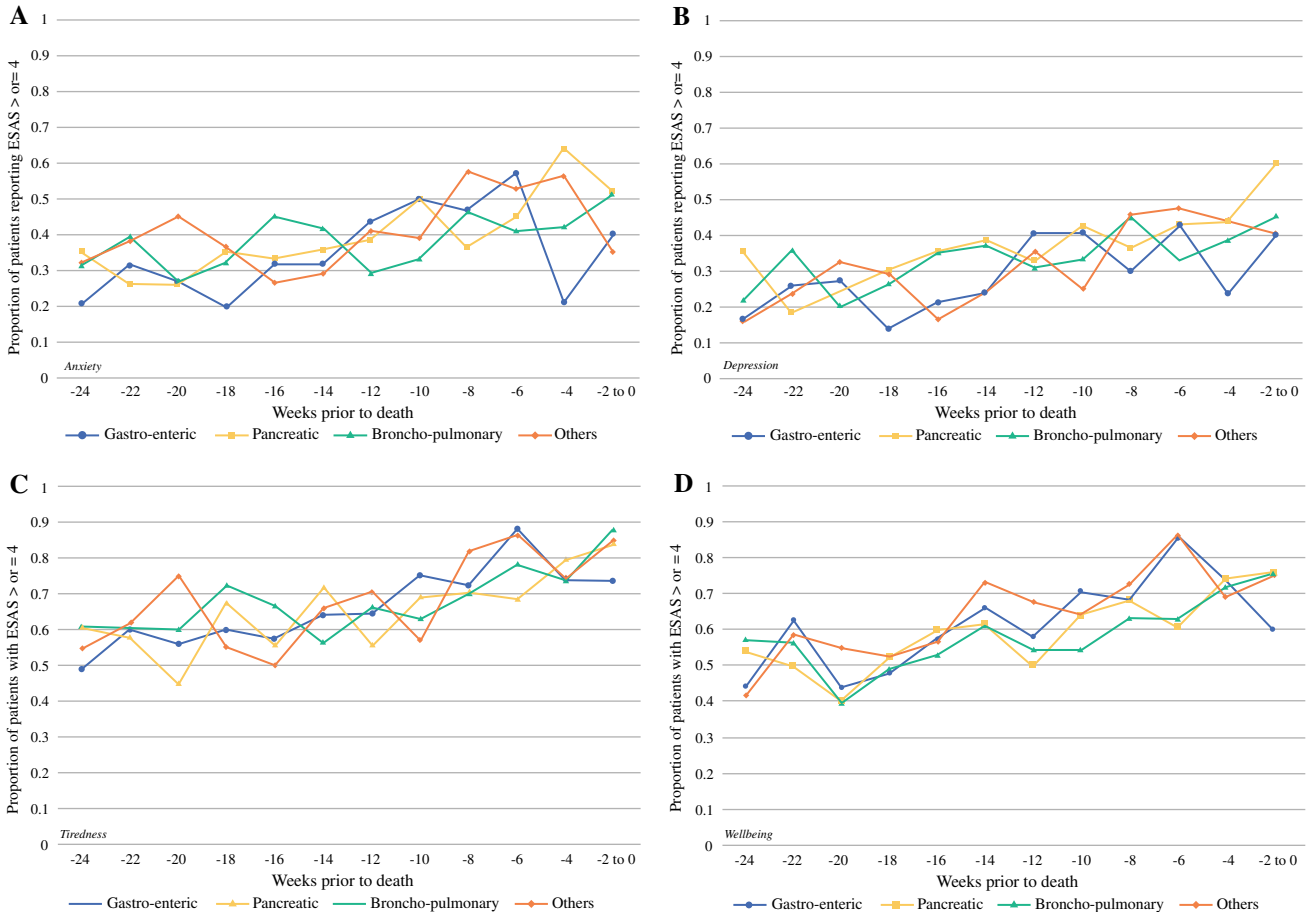


FIG. 4 Proportion of patients with NETs reporting moderate-to-severe (≥ 4) symptoms on the ESAS score in the last 6 months of life, stratified by primary tumor site, i.e. **a** anxiety, **b** depression, **c** tiredness, and **d** overall wellbeing. Trend lines do not represent continuous data but are included to facilitate the visualization of trends over time by symptom. *NETs* neuroendocrine tumors, *ESAS* Edmonton Symptom Assessment System

difficulty in accessing specialized cancer care and being retained in the healthcare system.[4,11] A higher proportion of NET patients reported moderate-to-severe symptoms on ESAS scores in the last 2–3 months of life compared with a previously published cohort of 100,000 cancer decedents. While those cancer decedents were observed to have stable rates of symptoms at the end-of-life, the reporting of moderate-to-severe symptoms in NETs increased as death approached.[21] This points towards a gap in symptom management for NETs compared with other cancers, possibly due to access to care issues or different underlying mechanisms requiring more tailored treatments. This study highlights the different needs for NETs at the end of life that cannot be fully appreciated or addressed when studied with other cancer types.

Routine symptom screening is key in ensuring early detection of symptoms and monitoring the impact of interventions. High symptom scores or an increase in symptoms should trigger early interventions, including referral to palliative care and psychiatry services, and advanced care planning. Palliative care resources remain underutilized, with up to two-thirds of cancer patients not benefiting from these resources.[32,36] Specialized multidisciplinary care models for NET patients should look beyond the provision of oncology care and should include early involvement of allied health support, not only for patients with new diagnosis but also for those with prolonged disease and close to the end of life. More frequent and earlier assessment by palliative care appears needed to offer better supportive therapy, whether standard of care supportive interventions available for other cancers (e.g. pain and nausea control, social support) or treatments specific to potentially endocrine-related symptoms, with somatostatin analogs or newly available inhibitors of tryptophan hydroxylase.

Predictors of moderate-to-severe symptoms can be used to identify patients at risk of inferior patient-centred outcomes. Women are at particularly increased risk of reporting high symptom burden, which is consistent with reports of differential symptom reporting for women after

TABLE 2 Multivariable analysis of the association between patient and tumor characteristics with moderate-to-severe (≥ 4) symptoms on the ESAS score in the last 6 months of life for patients with NETs (anxiety, depression, drowsiness, lack of appetite, and nausea)

Variable	Value	Anxiety		Depression		Drowsiness		Lack of appetite		Nausea	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Age, years	40–59	1.07	0.68–1.69	1.04	0.60–1.80	0.93	0.66–1.31	1.07	0.79–1.46	1.46	0.65–3.30
Ref: 18–39	60–79	1.02	0.65–1.60	0.97	0.57–1.67	0.92	0.65–1.28	1.09	0.80–1.47	1.23	0.54–2.77
	80–99	0.92	0.56–1.51	1.08	0.60–1.94	0.95	0.66–1.38	1.14	0.83–1.58	1.08	0.45–2.55
Female sex		*1.30*	*1.12–1.50*	1.18	0.99–1.39	1.02	0.91–1.14	1.07	0.96–1.18	*1.30*	*1.06–1.61*
Ref: Male											
Urban living		1.16	0.87–1.56	1.01	0.73–1.40	1.13	0.87–1.48	1.13	0.87–1.48	1.33	0.88–2.01
Ref: Rural											
Socioeconomic status (quintile)	First (lowest)	0.79	0.61–1.02	1.07	0.81–1.42	*0.82*	*0.68–1.00*	0.95	0.81–1.12	1.00	0.72–1.40
	Second	1.10	0.89–1.35	1.20	0.92–1.56	0.90	0.76–1.05	1.01	0.87–1.17	1.07	0.78–1.46
Ref: Fifth (highest)	Third	1.02	0.81–1.27	1.02	0.77–1.36	*0.80*	*0.66–0.95*	0.88	0.74–1.04	0.96	0.69–1.33
	Fourth	0.91	0.73–1.13	1.14	0.88–1.48	0.95	0.81–1.11	0.95	0.82–1.10	0.97	0.71–1.33
High comorbidity burden (ACG score ≥ 10)		1.16	0.99–1.37	1.09	0.90–1.31	1.13	1.00–1.28	1.01	0.90–1.13	1.22	0.97–1.54
Ref: ACG score 0–9											
Primary tumor site	Gastroenteric	0.91	0.74–1.12	0.86	0.68–1.10	0.90	0.77–1.05	1.04	0.90–1.21	1.22	0.91–1.64
Ref: bronchopulmonary	Pancreatic	1.06	0.86–1.30	1.10	0.87–1.39	0.90	0.76–1.06	1.09	0.94–1.27	1.31	0.96–1.78
	Others	1.05	0.86–1.29	0.95	0.75–1.22	1.04	0.89–1.22	1.10	0.96–1.26	1.33	0.99–1.80
Metastases at the time of death		0.98	0.82–1.17	1.06	0.87–1.30	0.93	0.81–1.07	1.03	0.90–1.17	1.00	0.77–1.29
Ref: None											
Date of death after 2012		0.91	0.78–1.06	0.97	0.81–1.16	1.01	0.90–1.14	0.92	0.83–1.03	1.04	0.83–1.30
Ref: before 2012											
Therapy over the course of disease	Chemotherapy	*0.82*	*0.71–0.93*	0.88	0.76–1.03	0.94	0.84–1.-5	0.90	0.80–1.00	0.87	0.70–1.08
Ref: No therapy	Local invasive therapy[a]	1.06	0.64–1.75	1.01	0.56–1.80	1.03	0.59–1.77	0.81	0.50–1.29	0.68	0.26–1.75
	Radiotherapy	0.86	0.71–1.05	0.95	0.77–1.16	1.09	0.95–1.24	0.96	0.85–1.10	0.99	0.75–1.30
Survival time from diagnosis, months	0–6	*1.22*	*1.01–1.47*	1.10	0.88–1.37	1.04	0.90–1.21	*1.19*	*1.03–1.37*	1.19	0.90–1.59
	7–12	0.88	0.71–1.11	0.83	0.64–1.08	*0.72*	*0.61–0.86*	1.02	0.87–1.19	1.00	0.74–1.34
Ref: ≥ 25	13–24	0.90	0.72–1.12	0.87	0.67–1.11	0.86	0.73–1.02	1.08	0.93–1.26	0.95	0.70–1.29
Number of months before death	1	*1.41*	*1.18–1.69*	*1.78*	*1.45–2.19*	*1.65*	*1.40–1.93*	*1.51*	*1.30–1.76*	*1.48*	*1.10–1.99*
	2	*1.33*	*1.13–1.57*	1.54	1.27–1.87	*1.41*	*1.21–1.64*	*1.32*	*1.14–1.53*	*1.50*	*1.13–1.98*
Ref: 6	3	1.16	0.98–1.37	1.37	1.12–1.67	*1.20*	*1.04–1.38*	*1.22*	*1.05–1.41*	*1.37*	*1.05–1.79*
	4	1.01	0.85–1.19	*1.17*	*0.96–1.43*	1.08	0.92–1.26	1.09	0.93–1.27	1.07	0.80–1.43
	5	0.86	0.73–1.01	0.97	0.79–1.19	1.02	0.88–1.19	1.00	0.86–1.17	0.78	0.58–1.05

Italics represent statistically significant associations

NETs neuroendocrine tumors, *ESAS* Edmonton Symptom Assessment System, *ACG* Aggregated Clinical Group, *RR* relative risk, *CI* confidence interval

[a]Includes surgery and liver embolotherapy

cancer diagnoses.[20,37] Of note, metastatic status at the time of death did not influence reporting of high symptom burden at the end of life, likely due to the unique biology of NETs whereby metastases may be present for years prior to death. Proximity to death is the factor most consistently associated with risk of reporting more severe symptoms. However, timing of death is difficult to prospectively define in clinical practice, potentially even more so for NET patients who experience a prolonged course of disease prior to death. Future research should focus on how to prospectively identify patients nearing death so that appropriate supportive care can be implemented. Screening and monitoring of patient-reported symptoms could potentially be included in tools to estimate the timing of death.

The main limitations of this study are the variation in the rates of patient-reported symptom screening in the population, and the retrospective definition of end of life. ESAS

TABLE 3 Multivariable analysis of the association between patient and tumor characteristics with moderate-to-severe (≥ 4) symptoms on the ESAS score in the last 6 months of life for patients with NETs (pain, shortness of breath, tiredness, overall wellbeing)

Variable	Value	Pain		Shortness of breath		Tiredness		Overall wellbeing	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Age, years	40–59	0.94	0.68–1.31	0.94	0.57–1.56	1.06	0.79–1.43	1.15	0.79–1.67
Ref: 18–39	60–79	0.81	0.58–1.12	0.94	0.57–1.54	1.11	0.83–1.49	1.13	0.78–1.64
	80–99	0.73	0.50–1.05	0.98	0.57–1.68	1.20	0.89–1.63	1.26	0.85–1.85
Female sex		*1.22*	*1.08–1.38*	0.97	0.83–1.13	1.08	1.00–1.16	1.06	0.97–1.16
Ref: Male									
Urban living		1.05	0.82–1.33	1.14	0.85–1.54	0.99	0.87–1.13	1.07	0.91–1.27
Ref: Rural									
Socioeconomic status (quintile)	First (lowest)	1.07	0.88–1.30	1.14	0.86–1.50	0.90	0.80–1.02	0.91	0.78–1.05
Ref: Fifth (highest)	Second	0.99	0.82–1.20	1.23	0.96–1.59	0.93	0.83–1.04	0.98	0.87–1.12
	Third	0.96	0.79–1.17	1.13	0.87–1.47	0.96	0.86–1.07	0.97	0.85–1.10
	Fourth	0.94	0.77–1.14	1.07	0.82–1.39	0.94	0.84–1.05	0.94	0.83–1.08
High comorbidity burden (ACG score ≥ 10)		1.05	0.92–1.20	1.15	0.98–1.36	1.07	0.99–1.17	1.05	0.95–1.15
Ref: ACG score 0–9									
Primary tumor site	Gastroenteric	*0.82*	*0.68–0.98*	*0.62*	*0.50–0.78*	0.91	0.82–1.01	1.00	0.88–1.13
Ref: bronchopulmonary	Pancreatic	0.87	0.72–1.06	*0.53*	*0.42–0.67*	0.97	0.88–1.08	1.01	0.89–1.15
	Others	1.16	0.99–1.35	*0.71*	*0.57–0.87*	1.04	0.95–1.15	1.09	0.97–1.23
Metastases at the time of death		0.99	0.85–1.16	*0.81*	*0.68–0.96*	0.93	0.85–1.02	1.00	0.90–1.12
Ref: None									
Date of death after 2012		*0.87*	*0.77–.099*	0.99	0.84–1.17	1.08	1.00–1.16	0.99	0.91–1.09
Ref: before 2012									
Therapy over the course of disease	Chemotherapy	*0.86*	*0.76–0.97*	0.95	0.83–1.09	0.94	0.87–1.02	0.94	0.86–1.03
Ref: No therapy	Local invasive therapy[a]	0.71	0.36–1.41	0.76	0.39–1.48	0.99	0.76–1.3-	1.14	0.84–1.53
	Radiotherapy	0.98	0.85–1.13	0.89	0.75–1.04	1.03	0.93–1.12	0.94	0.83–1.07
Survival time from diagnosis, months	1–6	0.99	0.83–1.18	0.96	0.76–1.21	0.99	0.90–1.09	1.07	0.96–1.20
Ref: ≥ 25	7–12	0.85	0.71–1.01	0.94	0.75–1.17	*0.88*	*0.80–0.98*	0.91	0.80–1.04
	13–24	0.86	0.72–1.02	0.89	0.70–1.13	*0.87*	*0.77–0.98*	0.93	0.82–1.06
Number of months before death	1	*1.50*	*1.27–1.77*	*1.87*	*1.53–2.29*	*1.40*	*1.26–1.56*	*1.40*	*1.23–1.58*
Ref: 6	2	*1.35*	*1.15–1.57*	*1.47*	*1.20–1.78*	*1.30*	*1.18–1.43*	*1.27*	*1.13–1.44*
	3	*1.21*	*1.04–1.41*	*1.34*	*1.10–1.62*	*1.16*	*1.05–1.28*	1.10	0.97–1.24
	4	1.06	0.90–1.25	1.16	0.95–1.41	1.07	0.97–1.19	1.09	0.96–1.24
	5	1.01	0.87–1.17	1.06	0.89–1.26	1.08	0.98–1.19	0.89	0.78–1.01

Italics represent statistically significant associations

NETs neuroendocrine tumors, *ESAS* Edmonton Symptom Assessment System, *ACG* Aggregated Clinical Group, *RR* relative risk, *CI* confidence interval

[a]Includes surgery and liver embolotherapy

scores were not collected at all institutions over the study period, which reflects the gradual implementation of the provincial program. This may impact the generalizability of the results. Furthermore, while this represents a large cohort of NETs, the availability of ESAS scores at each time point prior to death limited the number of patients to stratify the analysis further than by primary tumor site categories. Thus, differences between primary organs, such as pancreas compared with small intestine, could not be explored. End of life was retrospectively defined as the 6 months prior to death. It was not possible to define when patients were clinically identified as being at the end of life, nor was it always possible to identify this a priori in practice. While this challenges the timely implementation of supportive interventions, it outlines the need to develop tools estimating the time of death. Another limitation is the heterogeneity of NETs; this analysis did not divide NETs beyond primary tumor type categories in order to avoid

small numbers in subgroups. It was not possible to look at the symptom scores stratified by tumor grade or stage since this information was not available in the OCR. Metastatic status was used as a surrogate for advanced disease. Finally, while ESAS is not an NET-specific PRO, it was developed as an end-of-life assessment tool, has been validated in cancer patients, and can be used in clinics to screen for patients in need of more in-depth assessments and interventions. No NET-specific PRO is currently available. Future work could focus on developing NET add-ons for existing validated cancer PROs, to either provide further evaluation of high symptoms identified with the general PRO, or routinely assess specific symptoms such as those associated with carcinoid syndrome and cognitive disorders.

CONCLUSION

This study identifies a high prevalence of moderate-to-severe symptoms for NET patients at the end of life, not previously described, using prospectively validated scores. The proportion of moderate-to-severe symptoms increases steeply as death nears, highlighting an opportunity for improved and earlier supportive care. Combined with identified factors associated with moderate-to-severe symptoms, this represents valuable information to understand the NET patient experience at the end of life to provide individualized supportive care and assess the effectiveness of symptom management for an uncommon cancer. It provides a framework for future studies that should focus on developing tools to prospectively identify NETs at the end of life and defining the most effective early supportive care strategy.

ACKNOWLEDGMENT This study was supported by an unrestricted grant to the Sunnybrook Foundation by the NANETS Clinical Investigator Scholarship, Ipsen Biopharmaceuticals Canada, and the Sherif and Mary-Lou Hanna Chair in Surgical Oncology. The funding source had no role in the design, conduct, or interpretation of this study. This study was also supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by the ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI; however, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI. Parts of this material are also based on data and information provided by CCO. The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

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