

Original Article

Changes in Symptom Intensity Among Cancer Patients Receiving Outpatient Palliative Care

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Abstract

Context. Symptom changes are usually reported using summary statistics such as mean and/or median, which may obscure the treatment effect.

Objectives. The main objective of this retrospective study was to determine the magnitude of symptom changes as assessed by the Edmonton Symptom Assessment System (ESAS) after outpatient palliative care at the first follow-up visit.

Methods. We reviewed 1612 consecutive patients with cancer who were referred to the outpatient Supportive Care Center and who completed the ESAS at the initial and first follow-up visits between January 2003 and December 2010. All patients received interdisciplinary care led by the palliative care specialists following an institutional protocol.

Results. The distribution of the magnitude of symptom changes was stratified by baseline intensities. Patterns were similar for different ESAS items. At the follow-up visit (median: 15 days later), 52–74% of patients showed a decrease of one or more points in the ESAS score. However, 48–80% of patients with moderate/severe intensity at baseline complained of symptoms with an ESAS score of four or more after outpatient palliative care. Symptoms with absent/mild intensity worsened, ranging from a mean of -3.04 to 0.12 at the first follow-up visit, whereas symptoms with moderate/severe intensity improved from -0.2 to 3.86 ($P < 0.001$).

Conclusion. A considerable proportion of patients with moderate or severe intensity at baseline still had symptoms with an ESAS score of four or more. Patients with absent/mild intensities at baseline complained of symptom

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Key Words

Symptom, symptom intensity, assessment, outpatient, palliative care

Introduction

Patients with advanced cancer commonly have various physical and psychological symptoms such as pain, fatigue, depression, and anxiety.^{1,2} To assess these symptoms in patients with cancer, our team developed a tool known as the Edmonton Symptom Assessment System (ESAS).^{3,4} The ESAS includes nine common symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, anorexia, and feeling of well-being) and one patient-specific symptom. Symptom intensity is assessed using an 11-point numeric rating scale (NRS) ranging from zero (no symptom) to 10 (the worst possible severity). Sleep disturbance was adopted for the optional item at The University of Texas M. D. Anderson Cancer Center palliative care clinics, and the palliative care team routinely evaluates the ESAS scores of patients, using a standardized interdisciplinary approach in the outpatient setting. The ESAS has been widely used in clinical practice since its introduction and has been validated as an easy and reliable instrument for the assessment of symptoms in various populations and countries.^{5–8}

Tracking symptom changes in patients with cancer is essential to establishing symptom response criteria. It also helps in our understanding of the dynamic nature of cancer symptoms, which often follow an “up and down” course rather than a static course.⁹ In other words, a particular symptom may increase in frequency and severity during the course of disease and then decrease at the end of life and vice versa for other symptoms.¹⁰ Although the positive role of palliative care in symptom management for patients with cancer has been well documented,^{11,12} data regarding detailed changes in ESAS symptoms following outpatient palliative care (OPC) are very limited.

The main objective of this retrospective study was to determine the magnitude of

symptom change as assessed by the ESAS after OPC at the first follow-up visit. We hypothesized that the interdisciplinary approach by the OPC team reduces the symptom burden in patients with advanced cancer.

Methods

Patient Selection

We obtained approval from the institutional review board for this retrospective study, with waiver of informed consent. Eligible patients were at least 18 years old and had to have prospectively completed an ESAS questionnaire at both the initial visit and a follow-up visit within 30 days of the initial visit. We reviewed consecutive electronic medical records of patients seen at the OPC clinic. These patients had at least one follow-up visit after the initial consultation between January 2003 and December 2010. Of the 1869 screened patients, 1612 met the eligibility criteria; 257 patients did not have the follow-up visit within 30 days or less of the initial visit or had only a baseline visit. We gathered and analyzed information about the 1612 patients' demographic characteristics and change in symptoms using the ESAS scale at the follow-up visit after interdisciplinary OPC.

OPC Service

Care in the M. D. Anderson Supportive Care Center is provided by an interdisciplinary palliative care team led by board-certified palliative care specialists. The team members include a registered nurse with specific training in palliative care, a pharmacist, a nutritionist, a chaplain, a social worker, a palliative care and psychiatric nurse counselor, and a wound care nurse. These members provide mutual coverage in cases of absence or illness so that there are never clinic cancellations. This helps the team maintain a homogeneous approach

to assessment, management, and communication with patients and their families. The care by team members was provided following a standardized management guideline.¹³ After assessment of the patient's symptoms at every visit, the findings were then discussed with a palliative care specialist. On the basis of these findings, an interview was subsequently conducted with the patient and family. A physical examination also was performed. The physician and nurse requested appropriate members of the interdisciplinary team to participate in patient care as the patient's and family's individual needs on the occasion demanded.

Outcome Measures

In accordance with our standard protocol, patients completed the ESAS questionnaire whenever they visited the outpatient center. All questionnaires were completed by the patients or read to them by a nurse or caregiver. A palliative care-trained nurse helped patients to understand the questionnaire in cases when patients did not grasp the meaning. Symptom distress burden was determined by the sum of the ESAS score and defined as the symptom distress score.

The severity of symptoms was defined by using the following four intensity subgroups, following the work of Swarm et al.¹⁴ and Selby et al.¹⁵: NRS 0 = absent, 1–3 = mild, 4–6 = moderate, and ≥ 7 = severe. Symptoms of moderate or severe intensity were defined as clinically significant symptoms.

Symptom Changes

Symptom changes are usually reported with summary statistics such as mean and/or median with standard deviation concerning the whole population. We report the magnitude of symptom change as distribution stratified by the baseline symptom intensities (absent, mild, moderate, and severe) following the studies by Selby et al.¹⁵ and Follwell et al.¹⁶ A positive value indicates symptom improvement, whereas a negative value signifies symptom aggravation.

Statistical Analyses

Descriptive statistics (means, medians, frequencies, and percentages) were used to summarize the patients' demographic characteristics.

Demographic variables of interest were age, sex, race, and tumor site. The proportions of patients responding according to the four intensity subgroups were calculated for the individual ESAS symptoms. The Wilcoxon rank-sum test was used for age and the ESAS; the χ^2 test was used for sex, race, and primary cancer site. The paired *t*-test was used to analyze changes in symptom scores between baseline and follow-up visit. To examine intergroup differences for each symptom, the analysis of variance test was used. All *P*-values were two-sided, and *P*-values less than 0.05 were considered to indicate statistical significance. All analyses were performed using SPSS v. 15.0 (SPSS Inc., Chicago, IL) or SAS v. 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

Of the 1869 screened patients, 1612 patients met the inclusion criteria. Table 1 compares the characteristics of the 1612 eligible patients and the 257 ineligible patients. Age and sex did not differ statistically between the two groups, whereas race and primary tumor site were statistically different. Ineligible patients had significantly fewer symptoms than the eligible group at baseline (Table 1). Most of the ineligible patients were disqualified because of the absence of a follow-up visit. Some other characteristics of the 1612 eligible patients have been reported elsewhere.¹⁷ The median duration between referral to the palliative care team and the first follow-up visit was 15 days (quartile 1–3, 7–21).

Baseline Symptom Intensity

Fig. 1 shows the baseline ESAS symptoms categorized into absent, mild, moderate, and severe subgroups. The proportions of patients with clinically significant symptoms (NRS ≥ 4) were: pain 71%, fatigue 85%, nausea 27%, depression 40%, anxiety 43%, anorexia 52%, drowsiness 62%, well-being 70%, shortness of breath 38%, and sleep disturbance 62%.

Symptom Changes

Fig. 2 shows the detailed response to OPC from baseline symptom intensity at the first follow-up visit (a positive number means improvement and a negative number represents

Table 1
Comparison of Characteristics Between Eligible and Ineligible Patients

Characteristics	Eligible Patients (N= 1612)	Ineligible Patients (N= 257)	Pvalue
Age, mean (SD)	59.2 (13.2)	59.2 (14.0)	0.98
Sex, male, n (%)	846 (52)	134 (52)	0.92
Race, Caucasian, n (%)	1175 (73)	203 (79)	0.03
Primary cancer diagnosis, n (%)			
Lung	335 (21)	70 (27)	<0.01
Gastrointestinal	301 (19)	48 (19)	
Genitourinary	176 (11)	36 (14)	
Breast	128 (8)	12 (5)	
Head and neck	124 (8)	26 (10)	
Gynecologic	115 (7)	21 (8)	
Hematologic	77 (4)	15 (6)	
Others	356 (22)	29 (11)	
ESAS, median (Q1–Q3)			
Pain	6 (3–8)	3 (1–5)	<0.001
Fatigue	6 (5–8)	2 (0–3)	
Nausea	1 (0–4)	0 (0–1)	
Depression	3 (0–5)	0 (0–2)	
Anxiety	3 (0–5)	0 (0–3)	
Drowsiness	4 (1–6)	0 (0–2)	
Anorexia	5 (2–7)	2 (0–4)	
Feeling of well-being	5 (3–7)	2 (0–4)	
Shortness of breath	2 (0–5)	0 (0–3)	
Sleep	5 (2–7)	2 (0–4)	
Symptom distress score	40 (29–52)	21 (12–30)	

SD = standard deviation; ESAS = Edmonton Symptom Assessment System.

aggravation. A percent indicates the corresponding proportion of patients among 1612 patients). These results indicate a strong trend of symptom improvement (toward the right) in the patients with baseline moderate/severe intensity at the first follow-up visit and deterioration (toward the left) in the patients with baseline absent/mild intensity.

Table 2 shows that 52–74% of patients had improvement of their symptom intensity after

the OPC visit. However, 48–80% of patients with moderate or severe symptoms at baseline still had clinically significant symptoms (NRS ≥ 4) at the first follow-up visit. Of these “responder” patients with moderate/severe symptom intensity at baseline, 18–32% of the patients still had clinically significant pain at the follow-up visit.

The magnitude of the symptom changes shifted depending on baseline symptom

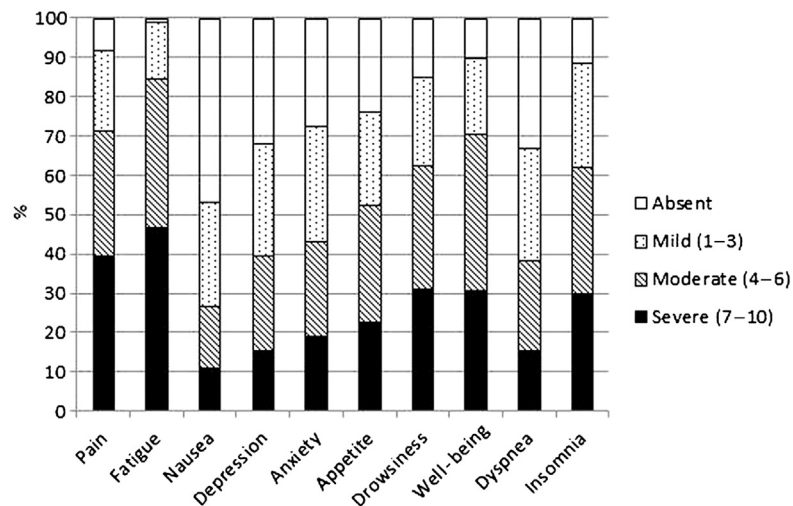


Fig. 1. Baseline Edmonton Symptom Assessment System values for the 1612 patients.

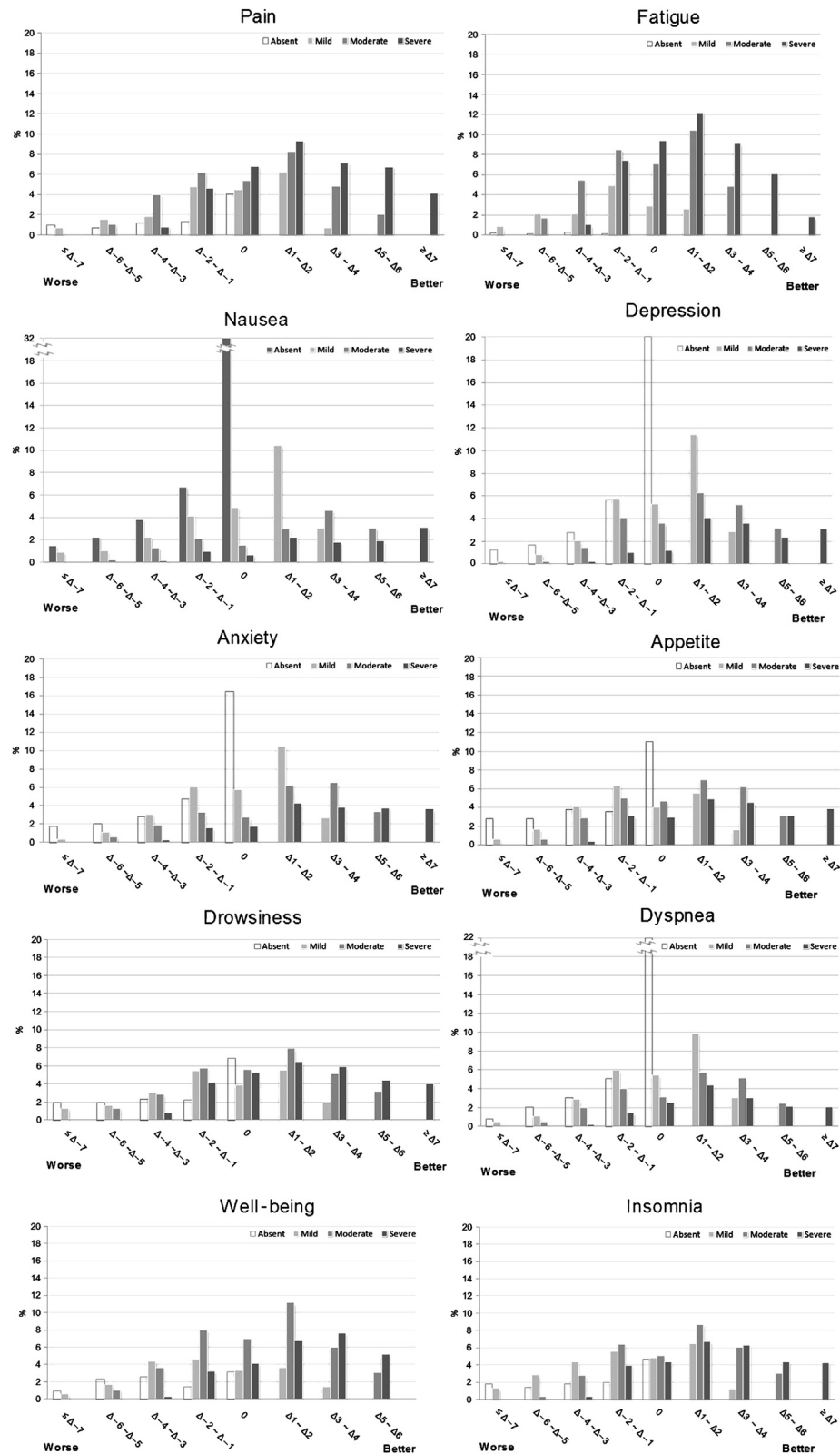


Fig. 2. Edmonton Symptom Assessment System score differences at the first follow-up visit according to the level of initial symptom intensity. Positive differences denote improvement (better); negative differences denote deterioration (worse) ($N=1612$).

Table 2
ESAS Changes in Patients With NRS ≥ 4 at Baseline

ESAS Item	N (%)	NRS ≥ 4 at Baseline				NRS ≥ 4 at Baseline and NRS ≥ 4 at Follow-Up
		N (%) With NRS ≥ 1 Point Improvement	Median at Baseline (Q1–Q3)	Median at First Follow-Up (Q1–Q3)	P-value	N (%)
Pain	1150 (71)	683 (59)	7 (5–8)	5 (3–8)	<0.001	801 (70)
Fatigue	1362 (84)	715 (52)	7 (5–8)	5 (4–8)	<0.001	1089 (80)
Nausea	432 (27)	318 (74)	6 (5–7)	5 (0–6)	<0.001	206 (48)
Depression	638 (40)	448 (70)	6 (5–7)	5 (2–6)	<0.001	355 (56)
Anxiety	696 (43)	504 (72)	6 (5–8)	5 (2–6)	<0.001	376 (54)
Anorexia	841 (52)	526 (63)	6 (5–8)	5 (2–7)	<0.001	523 (62)
Drowsiness	1005 (62)	593 (59)	6 (5–8)	5 (3–7)	<0.001	695 (69)
Well-being	1132 (70)	696 (61)	6 (5–8)	5 (3–7)	<0.001	771 (68)
Dyspnea	617 (38)	399 (65)	6 (5–8)	5 (2–7)	<0.001	366 (59)
Sleep disturbance	1003 (62)	632 (63)	6 (5–8)	5 (3–7)	<0.001	649 (65)

SD = standard deviation; NRS = Numeric Rating Scale.

intensity. In general, symptoms were exacerbated in absent/mild groups and improved in moderate/severe groups. All symptoms improved in the severe group, and there was a trend toward exacerbation in the absent/mild symptom group (Table 3). Symptoms with absent/mild intensity worsened, ranging from a mean of -3.04 to 0.12 at the first follow-up visit, and symptoms with moderate/severe intensity improved from -0.2 to 3.86 ($P < 0.001$).

Discussion

In this study, we documented symptom changes in patients with cancer after OPC at the first follow-up under the care of a team palliative medicine specialist. Most patients experienced a highly significant improvement in all symptoms after one single visit to an OPC clinic. These encouraging results support the value of delivery of OPC.

We find two meaningful results in this study. First, the magnitude of change tended to depend on baseline symptom intensity. Symptoms with absent/mild intensity generally were aggravated at the next follow-up visit (median: 15 days), whereas symptoms with moderate/severe intensity generally improved. This improvement was prominent in patients with severe symptoms at baseline, and the range of improvement was from 1.79 (fatigue) to 3.86 (nausea) (Table 3). A small but significant proportion of patients (ranging from 12% to

16%) who were free of pain, anorexia, or drowsiness at baseline experienced symptom exacerbation to a severe intensity at first follow-up. This result suggests that patients with absent or mild symptoms at baseline may experience increased symptoms in the near future. Considering the variety of these symptoms in patients with advanced cancer, assessment using a comprehensive tool such as the ESAS should be performed routinely at every visit.

Patients with less disease burden at the time of consultation may develop increased symptoms by the first follow-up because of disease progression; those with more severe symptoms at baseline could have a better chance for symptom relief by the first follow-up visit. A pilot study by Hwang et al.¹⁸ of 67 patients with advanced cancer showed progressive symptom deterioration using Karnofsky Performance Status scores, Functional Assessment of Cancer Therapy scores, and Memorial Symptom Assessment Scale-Short Form scores during the last six months of life. An observational cohort study by Seow et al.¹⁹ done in Ontario with 45,118 patients showed symptom trajectories according to ESAS symptom score. The authors analyzed the whole patient population and subgroups with moderate-to-severe symptoms, and they showed a similar trajectory of symptoms in both groups. However, they did not analyze the relationship between symptom severity and disease characteristics, and they did not analyze the symptom trajectory of patients with absent or mild symptoms. Further

Table 3
Changes in Symptoms Stratified by Baseline Intensity

Parameters	Intensity	Number of Patients	Mean (SD) of Change	95% CI of Change	Pvalue ^a
Pain	Absent	135	-2.16 (2.8)	2.65, -1.68	<0.001
	Mild	327	-0.85 (2.4)	-1.11, -0.58	
	Moderate	511	0.35 (2.7)	0.12, 0.58	
	Severe	639	2.53 (2.9)	2.30, 2.75	
Fatigue	Absent	15	-2.87 (3.5)	-4.82, -0.92	<0.001
	Mild	234	-1.83 (2.5)	-2.15, -1.51	
	Moderate	611	-0.2 (2.4)	-0.38, -0.01	
	Severe	751	1.79 (2.5)	1.61, 1.97	
Nausea	Absent	756	-1.08 (2)	-1.22, -0.93	<0.001
	Mild	424	0.02 (2.4)	-0.21, 0.25	
	Moderate	256	1.84 (2.9)	1.49, 2.19	
	Severe	176	3.86 (3.2)	3.38, 4.34	
Depression	Absent	515	-1.18 (2.1)	-1.36, -1.00	<0.001
	Mild	458	0.12 (2.2)	-0.07, 0.32	
	Moderate	387	1.37 (2.6)	1.11, 1.63	
	Severe	251	3.49 (3)	3.12, 3.85	
Anxiety	Absent	445	-1.48 (2.3)	-1.69, -1.26	<0.001
	Mild	471	-0.2 (2.3)	-0.4, 0.01	
	Moderate	392	1.49 (2.8)	1.22, 1.77	
	Severe	304	3.48 (3)	3.14, 3.82	
Anorexia	Absent	385	-2.37 (2.9)	-2.66, -2.08	<0.001
	Mild	385	-1.02 (2.5)	-1.27, -0.76	
	Moderate	474	0.97 (2.7)	0.73, 1.22	
	Severe	367	2.89 (3.2)	2.56, 3.23	
Drowsiness	Absent	245	-2.47 (2.9)	-2.84, -2.10	<0.001
	Mild	361	-1.03 (2.8)	-1.33, -0.74	
	Moderate	506	0.65 (2.7)	0.41, 0.89	
	Severe	499	2.54 (3.1)	2.27, 2.81	
Well-being	Absent	165	-3.04 (2.6)	-3.44, -2.64	<0.001
	Mild	313	-1.36 (2.6)	-1.65, -1.07	
	Moderate	639	0.6 (2.5)	0.41, 0.80	
	Severe	493	2.85 (2.8)	2.6, 3.09	
Dyspnea	Absent	537	-1.08 (2)	-1.24, -0.91	<0.001
	Mild	457	-0.09 (2.2)	-0.29, 0.12	
	Moderate	366	1.08 (2.7)	0.8, 1.35	
	Severe	251	2.71 (2.9)	2.36, 3.07	
Sleep	Absent	185	-2.73 (3)	-3.17, -2.29	<0.001
	Mild	424	-1.33 (2.7)	-1.59, -1.07	
	Moderate	520	0.93 (2.5)	0.71, 1.15	
	Severe	483	2.73 (3)	2.47, 3.00	

SD = standard deviation; CI = confidence interval.

^aThe P-value indicates statistical analysis between stratified groups by baseline intensity.

studies should address the association between symptom expression and disease burden over time, especially after referral to a palliative care team with experience in the assessment and management of symptoms.

The rapid symptom changes also can be explained by the dynamic nature of symptoms. McClement et al.²⁰ asserted that symptom change can be expected to occur over time, and thus measuring time is important because of the dynamic nature of the phenomenon. Especially when the cancer trajectory approaches the terminal stage, fluctuating functional status and treatment interventions would influence symptom intensity and hence symptom levels may be subject to change.^{21,22}

The changeable symptom intensities also might justify a shorter follow-up time than two weeks. Such a shorter follow-up would help detect early aggravation of symptoms in patients who are not expecting this in the short term.

The other key finding was that 48–80% of patients with moderate/severe intensity at baseline still had clinically significant symptoms. These findings imply that symptom control may not be sufficient at the first follow-up, even in patients with improving symptoms (18–32% of these patients had clinically significant symptoms after OPC), and various strategies might be needed to optimize symptom improvement in patients with advanced cancer, such as using telephone calls or interactive

voice response (IVR) to improve communication between patients and health professionals. The regular use of IVR could aid in early symptom assessment and expedite treatment of symptoms.²³ More research is needed to characterize the potential effect of more intense patient follow-up on symptom control.

Our study also raises the issue of the necessity for an attainable goal in symptom control because palliative care patients had only a few follow-up visits as a result of the late trajectory of cancer, and complete freedom from symptoms could be an unrealistic target. Our team recently studied personalized pain goals from the perspective of the patient and confirmed that three points is the most desirable and feasible goal in pain management in OPC.²⁴ Our detailed reports about the efficacy of OPC could help physicians predict symptom trajectory and plan strategies for management in patients with cancer.

Our findings suggest that current reporting of cohort changes using mean and/or median values does not provide complete information on the rate of success of palliative care interventions. New methods for the evaluation of clinical response are needed. One preliminary study suggests that, in the case of pain, patient-based outcomes such as the “personalized pain goal”²⁴ might be used to determine the success rate of symptom interventions. More research is necessary to better define this very important area of clinical outcomes.

One limitation of our study is the lack of repeated follow-up. We showed in this study that symptoms in palliative care patients might not be controlled to a satisfactory level at the first follow-up. Thus, it can be hypothesized that repeated follow-up visits are needed to improve patients’ symptoms. Unfortunately, the data for subsequent follow-up visits were not available in our study. Follwell et al.¹⁶ found no significant difference in symptom intensity between the first week and subsequent four weeks of follow-up. Further prospective research that evaluates the effect of follow-up frequency on symptom intensity may be valuable. Another limitation is that there was a possibility that one ESAS item could influence another item. The phenomenon of so-called symptom clusters tending to develop at a similar time has been consistently reported.^{25–27} We did not analyze correlation between ESAS

symptoms and thus could not exclude the possibility that the symptom variability in our study arose from a clustering nature of symptoms. Although ESAS information was collected prospectively, this study also has the limitations that are inherent to retrospective analysis. Finally, one possible limitation of our finding that mild symptoms worsen, whereas severe symptoms improve is the phenomenon called “regression to the mean.” Although it is impossible to determine if this phenomenon played a role, we found that patients with moderate symptoms (which could potentially improve or worsen) consistently demonstrated an improvement (Fig. 2), suggesting that our clinic interventions are at least somewhat effective.

In conclusion, a considerable number of patients with moderate or severe intensity at baseline still had symptoms with an ESAS score of four or more, and patients with absent/mild symptoms at baseline had exacerbated symptom intensities at the first follow-up visit. More strategies such as IVR or intense follow-up are needed to optimize symptom control in advanced cancer.

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