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Retrospective review of symptoms and palliative care interventions in women with advanced cervical cancer

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Abstract

Objective: The objective of this study was to delineate and measure the symptom distress experienced by patients with advanced cervical cancer at the time of palliative care (PC) referral.

Methods: A total of 156 patients with advanced cervical cancer were referred to PC from 2010 to 2012. Of these, 88 patients had completed the Edmonton Symptom Assessment System (ESAS) and were included in the analysis.

Results: The mean age was 45 years (25–76), 47% were white, 18% were African American, and 33% were Hispanic. Fifty-one percent were married, 64% had no advance directives, and 75% had recurrent disease. Clinically significant symptoms recorded by patient reported outcome measurement (defined as ESAS scores ≥4) were pain (81%), anorexia (72%), a poor feeling of well-being (70%), fatigue (69%), and insomnia (54%). The chief complaint recorded for the

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Conflict of Interest Statement

The authors declare no conflicts of interest.

visit was pain in 94% of patients. According to the PC specialists' assessment, pain (96%), emotional distress (77%), and constipation (50%) were predominant symptoms. Various PC interventions including opioids, laxatives, and expressive supportive counseling were provided. Clinically significant symptoms including nausea, depression, anxiety, and feeling of well-being were significantly improved at follow-up visits.

Conclusion: More than half of patients with advanced cervical cancer were significantly burdened with pain, anorexia, a poor feeling of well-being, fatigue, insomnia, and constipation at the time of PC referral. This research is an integral step towards developing a standardized tool for assessing symptoms in women diagnosed with cervical cancer and thus maximizing effectiveness of patient centered care.

Keywords

advanced cervical cancer; symptom; palliative care intervention

Introduction

In the United States, approximately 12,900 women are diagnosed with cervical cancer every year, and 4,100 deaths are attributable to cervical cancer [1]. The incidence of cervical cancer has significantly decreased in recent years owing to primary, secondary, and tertiary preventions with the human papillomavirus vaccine, Pap tests, and the treatment of dysplasia [2]. However, cervical cancer is still the second leading cause of cancer death in women aged 40 years or younger in the United States and is the fourth leading cause of all cancer deaths worldwide [1, 3]. Unfortunately, women who have received inadequate or no screening for cervical cancer may present with advanced stage disease. As a result, they may have limited treatment options with compromised survival outcomes.

Apart from a poor prognosis, patients with advanced cervical cancer may experience a variety of distressing physical symptoms associated with the anatomic location of their disease and complications after surgery and/or radiotherapy. They may also experience distressing psychological symptoms related to their relatively young age and low socioeconomic status [4, 5]. Common physical symptoms include pain, fatigue, lymphedema, sexual dysfunction, proctitis, cystitis, constipation, diarrhea, foul odor, and fistulas [4–10]. Levels of depression and anxiety are significantly higher in cervical cancer patients than in the general population, and their quality of life is lower [11]. Decreasing the burden of these symptoms in cervical cancer patients may improve their quality of life and daily functioning [12]. Unfortunately, despite the tremendous impact symptoms can have on quality of life, there is no standardized tool for assessing symptoms of gynecologic cancer, and symptom assessment is rarely a part of routine cancer care [13].

The objective of this study was to delineate and measure the severity and frequency of multiple physical and psychological symptoms in patients with advanced cervical cancer at the time of referral to palliative care (PC) and to characterize the PC interventions that patients received. Supportive care interventions for women with cervical cancer are needed at almost every provider-patient interaction but often left unaddressed or not assessed until symptoms become extreme. Fortunately in some cases, women are then referred to palliative

care specialists. Few studies in the literature have focused only on the symptoms of women with active cervical cancer and all have been cross sectional in design [4–10]. Having this type of information will allow for a better understanding of what questions should be part of every provider's symptom assessment repertoire and allow for guidance in the design of effective clinical trials with supportive care endpoints.

Methods

Patients

Patients with advanced cervical cancer who were referred to PC specialists at The University of Texas MD Anderson Cancer Center from 2010 to 2012 were included in this study. Among 4,375 patients who visited the outpatient Supportive Care Center, 95 patients had cervical cancer, and among 4,072 patients who were referred to PC as inpatients, 97 had cervical cancer. In total, 192 consecutive referrals were identified, and 35 were duplicate visits. The unique total number of referral visits identified was 156. Patients were eligible for this study if they had a diagnosis of advanced cervical cancer, had completed the Edmonton Symptom Assessment System (ESAS), and were 18 years or older. We defined advanced cancer as metastatic or recurrent disease or progressive locally advanced disease not amenable to receive curative treatment. A total of 88 patients met the eligibility criteria and were included in the final analysis. Forty-one patients had follow-up visits to PC within 2 months of their first PC consultation. Thirty-five of the 41 patients completed the ESAS at follow-up visits, forming a subgroup of patients whose data could be analyzed for changes over time. The Institutional Review Board at the MD Anderson Cancer Center approved this study and waived the requirement for informed consent.

Palliative Care Service

An interdisciplinary team led by board-certified PC specialists provides PC at MD Anderson. The interdisciplinary team members include registered nurses with specific training in PC, pharmacists, a nutritionist, a chaplain, social workers, and psychologists. The care of all patients is provided using standardized management algorithms [14]. In the outpatient Supportive Care Center, patients and their families are initially assessed by the PC nurse using assessment tools such as the ESAS [15, 16]; Memorial Delirium Assessment Scale (MDAS) [17]; Cut down, Annoyed, Guilty, Eye opener (CAGE) questionnaire [18]; and Eastern Cooperative Oncology Group (ECOG) performance status [19]. The PC nurse discusses with the PC specialist the results of the initial assessment including ESAS scores, prescribed medications, and other findings. After the discussion, the physician conducts an interview and physical examination to assess the patient. The appropriate interdisciplinary team members, according to his/her individual needs, then care for the patient. Patients referred to the inpatient PC mobile team also receive initial assessments using the ESAS, MDAS, CAGE, and ECOG performance status and are treated on the basis of these assessments.

Data Collection

Demographic information including age, sex, ethnicity, marital status, and education level were collected from the patients' electronic medical records. The following additional

information was collected: disease status at the time of referral; cancer treatment status; setting of referral (inpatient vs. outpatient); history of depression or anxiety; morphine equivalent daily dose (MEDD); the presence of deep vein thrombosis (DVT); use of a ureteral stent, nephrostomy, or colostomy; date of advanced cancer diagnosis; date of death or last follow-up; and survival status.

In accordance with our standard clinic procedure, patients had documented ESAS, CAGE, and MDAS scores and ECOG performance status at the time of referral. The ESAS determines the severity of 10 symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, feeling of well-being, and insomnia) rated using a numerical scale of 0–10 (0, no symptoms; 10, worst possible symptoms) (Supplementary Table 1). Consistent with previous studies, symptoms of moderate or severe intensity (scores ≥4) were defined as clinically significant symptoms [20, 21]. The symptom distress score was defined as the sum of the scores of 9 items excluding insomnia [15, 22].

One gynecologic oncologist with a PC subspecialty (LMR) and 2 medical oncologists with PC training (YJK, JCP) intensively reviewed the first 12 charts to identify characteristics of symptom assessments and PC interventions provided by PC specialists. On the basis of this initial review of 12 charts, documented chief complaints, symptom assessments, and PC interventions were categorized (Table 3 and 4), and the remaining charts were reviewed according to these categories.

Statistical Analysis

The patient characteristics and symptom assessments were summarized using descriptive statistics including means, medians, frequencies, and percentages. Median ESAS scores were compared between two groups, those who received inpatient vs. outpatient consultations, using the Wilcoxon rank-sum test. Median survival and median time to PC consultation were calculated using the Kaplan-Meier method. Survival was calculated from the date of advanced cancer diagnosis or PC referral to the date of death or last follow-up, and groups were compared using the log-rank test. All tests were two-sided, and $P<0.05$ was considered statistically significant. Confidence intervals (CIs) were calculated at a 95% confidence level. All analyses were performed using IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA) or SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

A total of 88 patients with advanced cervical cancer referred to PC between January 1, 2010, and December 31, 2012, were eligible for this study. The mean patient age was 45 years (standard deviation [SD], 11; range, 25–76 years); 47% were white, and 51% were married. The majority of patients (75%) had recurrent disease; 19% of patients had newly diagnosed advanced cervical cancer and had not yet received treatment, 51% were receiving palliative chemotherapy, and 16% were not able to receive any more anti-cancer treatment. More than half of the patients (58%) were referred as inpatients and had an ECOG performance status of 3 or more (54%). Thirteen percent had a history of depression, and 18% had a history of anxiety; 20% had DVTs; 17% had ureteral stents; 17% had nephrostomies; and

7% had colostomies. None of the patients had a positive CAGE score, and 7% of patients had delirium according to the MDAS. The baseline patient characteristics at the time of referral are summarized in Table 1.

ESAS scores and the percent of patients with clinically significant scores (scores ≥4) are summarized in Table 2. The median ESAS pain score was 6 (interquartile range, 4–8), and 81% of patients had an ESAS pain score ≥4. Other clinically significant ESAS symptoms identified among these patients were anorexia (72%), a poor feeling of well-being (70%), fatigue (69%), and insomnia (54%). The chief complaint at the time of PC referral was pain in 94% of patients (Table 3). According to the PC specialists' medical records, pain (96%), emotional distress (77%), and constipation (50%) were the most common symptoms.

A variety of palliative interventions were provided to the patients (Table 4). Pharmacologic interventions included opioid analgesics (94%), laxatives (59%), antiemetics (32%), antipsychotics or antidepressants (14%), and steroids (11%). Regarding opioids, 36% of all patients had opioid initiation, 32% had opioid dose adjustment, and 13% had opioid rotation. Non-opioid analgesics were prescribed to 14% of the patients. Non-pharmacologic interventions included expressive supportive counseling (61%), end-of-life discussions (25%), physical exercise (13%), and various consultations with a psychiatrist, rehabilitation medicine team, counselor, social worker, or chaplain.

ESAS scores for dyspnea (1 vs. 0, P=0.003), nausea (2 vs. 0, P=0.018), and depression (4 vs. 1, P=0.021) were significantly higher in outpatient referrals than in inpatient referrals (Table 5). The median time from advanced cervical cancer diagnosis to PC consultation was 6.0 months (95% CI 5.0–7.8), and the median survival after the first PC visit was 4.8 months (95% CI 3.4–6.2). Survival after PC consultation was significantly lower in inpatient referrals than in outpatient referrals (4.1 vs. 6.2 months, P=0.007).

Clinically significant symptoms (ESAS scores ≥ 4) including nausea, depression, anxiety, and the feeling of well-being were significantly improved at follow-up visits (Table 6). With the exception of insomnia, scores for all other clinically significant ESAS symptoms showed a tendency to improve at follow-up visits. Among 41 patients with follow-up visits, the median MEDD was significantly higher at follow-up (60 vs. 90 mg, P=0.007).

Discussion

In this retrospective point of contact study, we found that in our center, women with advanced cervical cancer are relatively young, and more than 80% present to the PC consultation for moderate to severe pain. Furthermore, more than half also have moderate to severe anorexia, a poor feeling of well-being, fatigue, and insomnia. Although the majority of patients was receiving or planned to receive palliative chemotherapy at the time of PC referral, the median survival after the first PC consultation was only 4.8 months (95% CI 3.4–6.2). Patients who were referred to PC in the inpatient setting had significantly poorer survival than patients referred in the outpatient setting (4.1 vs. 6.2 months, P=0.007). Clinically significant moderate to severe symptoms (ESAS scores ≥4) had improved at follow-up visits.

The ESAS is a simple and reliable assessment tool to screen for the intensity of nine common symptoms and one optional symptom (insomnia in our center) experienced by cancer patients [15, 21]. The ESAS permits physicians to assess a patient's perceived symptoms and to obtain a profile of symptom severity at a point in time. Using a cutoff value of 4, physicians can quickly detect clinically significant symptoms with moderate to severe intensity [20, 21, 23]. In accordance with previous studies in advanced cancer patients, moderate to severe pain was highly prevalent in our patients, along with anorexia, a poor feeling of well-being, fatigue, and insomnia [21, 24, 25]. Accordingly, based on ASCO recommendations, these women should be considered for early palliative care referral in order to maximize QOL and performance status, potentially avoid inpatient management of uncontrolled symptoms, and potentially their ability to enroll in clinical trial investigations [26].

Interestingly, although the median ESAS scores for depression and anxiety were not high, emotional distress (77%) was the predominant symptom following pain, according to the PC physicians' assessment. Constipation (50%) was the next most common symptom assessed by physicians. As a result, the primary PC interventions provided to patients were pain control with opioids, constipation management, and expressive supportive counseling. Further studies will be needed to identify the symptoms that are not easily assessed by ESAS. In an attempt to assess the multidimensional aspects of emotional distress, we have been routinely screening for spiritual distress and financial distress along with the 10 ESAS symptoms in every patient since 2012 [27, 28].

Because the characteristics of cervical cancer patients include young age, relatively low socioeconomic status, and specific symptoms that are not covered by the ESAS, such as lymphedema, sexual dysfunction, proctitis, cystitis, diarrhea, foul odor, and fistulas, a more specified approach may be required to assess symptom distress in these patients. Limited data are available for symptom assessment tools that address gynecologic cancer-specific issues. Our group has validated the MD Anderson Symptom Inventory for ovarian cancer and is currently validating the MD Anderson Symptom Inventory for cervical cancer [29].

Patients with recurrent or metastatic cervical cancer that is resistant to platinum-based chemotherapy may experience various disturbing symptoms related to disease progression and/or treatment side effects. The survival benefit of second- or third-line treatments is unclear, and most patients have a limited survival of 6 to 8 months [5, 30]. In this patient population, reducing symptoms and maintaining quality of life may be the only goals of anti-cancer treatment. PC is known to improve patient outcomes in terms of symptom management [31]. Furthermore, several pivotal randomized clinical trials have shown that early integration of PC into standard oncology care can improve patients' quality of life, mood, and even survival [32–34]. The Society of Gynecologic Oncology now recommends that basic PC should not be delayed in women with advanced gynecologic cancer, and a referral for specialty-level PC should be provided whenever appropriate [35]. The American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines also recommend that PC should be integrated with standard oncology care for any patient with metastatic cancer [26, 36]. Therefore, regardless of the decision to administer further palliative chemotherapy, gynecologic oncologists should actively provide PC to ensure the

best possible quality of life for their patients. This may be done by using appropriate symptom assessment tools as part of their standard care and by referring patients to PC providers much earlier, especially patients with high symptom distress.

Reducing symptoms is essential not only for improving quality of life but also, potentially, for prolonging survival. In one study, the pretreatment patient-reported physical well-being as measured by the physical well-being subscale of the Functional Assessment of Cancer Therapy-Cervix was significantly associated with improved overall survival in clinical trials for advanced cervical cancer patients ($P<0.001$) [37]. Temel et al. reported that early integration of PC with standard oncology care in newly diagnosed advanced non-small cell lung cancer patients improved survival (11.6 vs. 8.9 months) despite less aggressive end-of-life care [33]. Enrollment in hospice may also be associated with prolonged survival [38].

Although it is not possible to draw definite conclusions owing to the small number of patients and retrospective nature of this study, all clinically significant symptoms except insomnia numerically improved at the first follow-up visits to PC. Nausea, depression, anxiety, and well-being improved significantly. This finding is in accordance with previous studies by our group that reported significant symptom improvements in terms of ESAS after the initial PC consultation [20, 21, 39]. However, the findings of the current study revealed significant but only partial improvement in several symptoms assessed by the ESAS between first and second supportive care assessments. These findings may suggest that patients with advanced cervical cancer need more than one follow-up visit to achieve major symptom relief. Follow-up visits should ideally take place within in short time intervals to facilitate rapid relief of physical and psychological distress.

In conclusion, pain was the primary symptom for patients with advanced cervical cancer at the time of PC referral along with anorexia, a poor feeling of well-being, fatigue, insomnia, and constipation. Clinically significant symptoms including nausea, depression, anxiety, and well-being significantly improved at follow-up visits. Early integration of PC may be important to prevent unnecessary distress or hospital admissions and potentially to improve survival.

We expect these data to be useful in identifying more important and meaningful clinical trial endpoints. The search for effective therapies in clinical trials should always be weighed against the impact on patients' quality of life and symptom improvement [5]. Clinical trial endpoints in advanced cervical cancer patients should be dual in nature and include not just drug efficacy on decreasing the tumor size but also on improving specific symptoms. Further studies are required to find a relevant strategy to encompass symptom distress as a clinical trial endpoint in women with incurable, but tragically preventable, cervical cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Advanced cervical cancer patients are burdened with various distressing symptoms
- Symptoms include pain, anorexia, poor feeling of well-being, fatigue and insomnia
- Many clinically significant symptoms improve at follow-up visits to palliative care

Table 1.

Patient characteristics at the time of palliative care referral

Variable	Number of patients *N*=88 (%)
Age, years, mean±SD	45±11 (rang, 25–76)
Race	
Caucasian	41 (47)
African American	16 (18)
Hispanic	29 (33)
Asian/Other	2 (2)
Marital status	
Single	25 (28)
Married	45 (51)
Separated/Divorced	13 (15)
Widowed	5 (6)
Education	
High school or below	28 (32)
Some college/associate degree	23 (26)
Bachelor degree	13 (15)
Advanced degree	7 (8)
Unknown	17 (19)
Initial FIGO stage	
IB1	15 (17)
IB2	12 (14)
IIA	4 (5)
IIB	18 (20)
IIIA	1 (1)
IIIB	12 (14)
IVA	2 (2)
IVB	18 (20)
Not reported	6 (7)
Disease status at the time of referral	
Initially metastatic disease (stage IVB)	18 (21)
Recurrent disease	66 (75)
Progressive locally advanced disease *	4 (4)
Cancer treatment status	
Newly diagnosed (not yet received treatment)	17 (19)
Palliative chemotherapy	45 (51)
Palliative radiotherapy	10 (11)
Palliative surgery	2 (2)
No more anti-cancer treatment	14 (16)
Setting of referral	

Variable	Number of patients *N*=88 (%)
Inpatient	51 (58)
Outpatient	37 (42)
ECOG performance status	
1	14 (16)
2	18 (20)
3	40 (46)
4	7 (8)
Not reported	9 (10)
History of depression	11 (13)
History of anxiety	16 (18)
CAGE positive (≥2)	0 (0)
Delirium by MDAS (≥7)	6 (7)
MEDD, median, mg/day [IQR]	60 [17.5–127.5]
Deep vein thrombosis	18 (21)
Ureteral stent	15 (17)
Nephrostomy	15 (17)
Colostomy	6 (7

Abbreviations: CAGE, Cut down/Annoyed/Guilty/Eye opener; ECOG, Eastern Cooperative Oncology Group; ESAS, Edmonton Symptom Assessment Scale; FIGO, International Federation of Gynecology and Obstetrics IQR, interquartile range; MDAS, Memorial Delirium Assessment Scale; MEDD, morphine equivalent daily dosing; SD, standard deviation

* Locally advanced disease indicates FIGO stage IB2 to IVA

Table 2.

Baseline ESAS scores *

Variable	Median (IQR)	Number of patients with ESAS score≥4 (%)
Pain	6 (4–8)	71 (81)
Fatigue	5 (3–8)	61 (69)
Nausea	1 (0–4)	25 (28)
Depression	2 (0–5)	32 (36)
Anxiety	3 (1–6)	39 (44)
Drowsiness	2 (0–5)	29 (33)
Dyspnea	0 (0–2)	18 (20)
Anorexia	5 (3–8)	63 (72)
Feeling of well-being	5 (3–7)	56 (70)
Sleep	4 (1–7)	47 (54)
Symptom distress score	34.5 (24–44)	-

Abbreviations: ESAS, Edmonton Symptom Assessment System; IQR, interquartile range

* Higher scores reflect worse symptomatology. Symptoms with ESAS scores ≥4 were considered as ‘clinically significant’ symptoms.

Table 3.

Documented chief complaints and symptom assessments by palliative care specialists

Variable	Number of patients (%)
Chief complaints	
Pain	83 (94)
Nausea/Vomiting	15 (17)
Constipation	7 (8)
Fatigue	6 (7)
Emotional distress	8 (9)
Other symptom	14 (16)
End-of-life care issues	2 (2)
Symptom assessment	
Pain	84 (96)
Nausea/Vomiting	34 (39)
Constipation	44 (50)
Anorexia	14 (16)
Fatigue	24 (27)
Dyspnea	4 (5)
Emotional distress	68 (77)
Depression	11 (13)
Anxiety	19 (22)
Insomnia	9 (10)
Delirium	3 (3)
Other symptom	19 (22)
End-of-life care issues	17 (19)
Family distress	2 (2)

Table 4.

Palliative care interventions prescribed by palliative care specialists

Interventions	Number of patients (%)
Pharmacological intervention	
Opioid analgesics	
Start opioid	32 (36)
Adjustment of opioid dose	28 (32)
Opioid rotation	11 (13)
No change in opioids	12 (14)
Non-opioid analgesics	
Acetaminophen	5 (6)
Gabapentin/pregabalin	7 (8)
Dexamethasone	10 (11)
Antiemetics	28 (32)
Laxatives	52 (59)
Antipsychotics or antidepressants	12 (14)
Non-pharmacological intervention	
Expressive supportive counseling	54 (61)
End-of-life care discussions	22 (25)
Exercise	11 (13)
Consultation	
Psychiatry	12 (14)
Rehabilitation	9 (10)
Counselor	7 (8)
Social worker	15 (17)
Chaplain	8 (9)

Table 5.

Comparison of baseline ESAS scores and time interval between events by setting of palliative care referral

Variable	Total, *N*=88	Inpatient referral, *N*=51	Outpatient referral, *N*=37	*P*
Pain	6	7	6	0.124
Fatigue	5	5	6	0.598
Nausea	1	0	2	0.018
Depression	2	1	4	0.021
Anxiety	3	3	3	0.939
Drowsiness	2	0	3	0.062
Dyspnea	0	0	1	0.003
Anorexia	5	5	5	0.230
Feeling of well-being	5	5	5	0.334
Sleep	4	3	5	0.090
Symptom distress score	34.5	32	36	0.119
Advanced cancer diagnosis to first palliative care consultation, median, months (95% CI)	6.0 (5.0–7.8)	5.9	6.0	0.970
Survival after advanced cancer diagnosis, median, months (95% CI)	15.6 (11.4–17.5)	13.8	20.0	0.027
Survival after first palliative care consultation, median, months (95% CI)	4.8 (3.4–6.2)	4.1	6.2	0.007

Abbreviations: CI, confidence interval

Table 6.

ESAS scores at baseline and follow-up visits

ESAS variable	Baseline ESAS score, median (IQR) N=35	FUESAS score, median (IQR) N = 35	*P*	Number of patients with baseline ESAS score≥4 (%)	Baseline ESAS score in patients with baseline ESAS≥4, median (IQR)	FUESAS score in patients with baseline ESAS≥4, median (IQR)	*P*
Pain	6 (4–8)	6 (3–9)	0.536	30 (85.7)	7 (6–8)	6.5 (4–8)	0.087
Fatigue	5 (3–8)	5 (3–7)	0.599	22 (62.9)	7 (6–8)	5 (4–8)	0.076
Nausea	1 (0–5)	1 (0–4)	0.502	11 (31.4)	6 (5–9)	3 (1–4)	0.006
Depression	2 (0–4)	1 (0–3)	0.174	13 (37.1)	5 (4–6)	2 (0–7)	0.042
Anxiety	3 (0–5)	1 (0–3)	0.078	16 (45.7)	5 (4–8)	2 (0–5)	0.004
Drowsiness	3 (0–5)	3 (0–4)	0.707	13 (38.2)	5 (5–7)	3 (3–5)	0.124
Dyspnea	0 (0–2)	0 (0–3)	0.660	6 (17.1)	5 (4–6)	2 (1–3)	0.063
Anorexia	5 (3–8)	5 (3–7)	0.787	22 (64.7)	6 (5–9)	5 (4–8)	0.100
Feeling of well-being	5 (3–7)	4 (3–7)	0.299	25 (73.5)	6 (5–7)	4 (3–7)	0.028
Sleep	4 (2–6)	5 (3–7)	0.257	18 (52.9)	6 (6–8)	7 (5–8)	0.887
SDS	33 (21–44)	27 (20–35)	0.167	---	---	---	---

Abbreviations: ESAS, Edmonton Symptom Assessment System; FU, follow-up; IQR, interquartile range;