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ORIGINAL ARTICLE

Symptom hyper-expression in advanced cancer patients with anxiety and depression admitted to an acute supportive/palliative care unit

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Abstract

Purpose The aim of this study was to compare symptom expression in advanced cancer patients with depression and anxiety and in patients with no such symptoms.

Methods Secondary analysis of a previous study assessing the role of an acute palliative supportive care unit (APSCU) in a comprehensive cancer center. Patients completed the Edmonton Symptom Assessment System (ESAS) at admission (T0) and 7 days after or at discharge (T7).

Results Three hundred-fourteen consecutive cancer patients admitted to the APSCU were surveyed. Eighty-six and 66 patients improved their level of depression and anxiety, respectively (passing from ≥ 4 to 0–3, from T0 to T7), after that palliative care intervention resulted in a significant improvement of the other symptoms. Changes were statistically significant for both symptoms ($P < 0.0005$). Patients admitted for uncontrolled pain were more likely to be anxious, while patients admitted for other symptoms or end-of-life care were more likely to be depressed. The presence of anxiety and depression (≥ 4/10 on ESAS) was significantly associated with a higher level of symptom expression at admission and at T7 ($P < 0.0005$). In patients presenting both psychological symptoms, symptom expression was significantly more relevant in comparison with patients not reporting moderate-severe psychological symptoms. Pain and depression were independently associated with anxiety at T0. Variables independently associated with depression at T0 were drowsiness, appetite, and anxiety.

Conclusions Psychological symptoms of ESAS concur to hyper-express some symptoms and make symptom control more difficult. A clear association between anxiety and depression exists.

Keywords Advanced cancer · Anxiety · Depression · Palliative care

Introduction

About 30% of palliative care patients have been identified as experience psychological distress [1, 2]. Psychological distress may decrease patients' compliance, functional status, while increasing hospital staying [1]. Patients with advanced cancer often experience psychological problems as their physical symptom worsen. Depression has been found to be an independent predictor of poor survival [1] although in another study, psychological symptoms did not result in shortening time to death [3]. On the other hand, depression may affect other symptoms commonly present in the advanced stage of

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disease [4] and may render symptom management more difficult [5]. Recent research from non-cancer patients suggests an interaction between medical and psychological factors [6, 7].

Studies in cancer population have focused on specific somatic symptoms, primarily pain and fatigue [3, 8, 9]. Depressive symptoms, however, may occur with pain and fatigue among cancer patients [9, 10]. It is likely that psychological factors play a role in over-expressing also other symptoms, other than pain and fatigue [7]. The relationship between psychological and somatic symptoms may change through the disease trajectory. Studies of depression in patients with advanced cancer have used a range of different assessment instruments [11].

Given these methodological issues, the inconsistent results of the few studies to date are perhaps not surprising [10, 12–14] regarding such a relationship. Despite consistent data report that poor prognosis is related to both increased somatic symptom burden [15] and depression, the potential effect of disease-related factors on symptom burden was considered in only one of these studies [12]. On the other hand, the assessment of depression in cancer populations is challenging, primarily because depressive symptoms may have multiple origins, including cancer, treatment, functional impairments [11], or primitive. For anxiety that is another relevant psychological symptom, data are really poor [16]**.** Thus, it remains unclear whether depression and anxiety are associated with, or may contribute to, increased somatic symptom burden among patients with advanced cancer. The aim of this study was to compare symptom expression in patients with depression and anxiety and in patients with no such symptoms. It has been hypothesized that patients with depression and/or anxiety report a higher symptom burden than those without.

Methods

This is a secondary analysis of a previous study assessing the role of an acute palliative/supportive care unit in a comprehensive cancer center [17]. The study was approved by the ethical committee and informed consent was obtained. Age, gender, educational level, Karnofsky level, and primary tumor were recorded. Awareness of prognosis for patients and relatives was assessed by semi-structured interviews (complete, partial, absent). Reasons for admission were recorded, as well as the kind of admission (unplanned or planned) or readmission. Data regarding caregivers were gathered. A caregiver was considered as a person who spent at least 4 h/day with the patient. Awareness of prognosis for patients and relatives was assessed by semi-structured interviews (complete, partial, absent). The following data were also recorded: patients still receiving anticancer treatment (on/off treatment or uncertain), or other anticancer treatments (radiotherapy, surgery, target therapy, hormonal therapy) received in the last 30 days, previous care setting (home, hospital unit, day-hospital, or other hospitals), and who referred the patient to the unit (general practitioner (GP), home palliative care physicians, oncologists, other units, or other hospitals). Patients completed the Edmonton Symptom Assessment System (ESAS) at admission (T0) and 7 days after or at discharge (T7). The ESAS consists of ten items that are rated 0 to 10 evaluating the intensity of physical and psychological symptoms and global sense of poor well-being [18–20]. The ESAS is easy to administer, requiring minimal effort and concentration from the patient and/or the surrogate.

Analgesics and their doses (expressed as oral morphine equivalents (OME)) at T0 and T7 were also recorded, as well as the duration of hospital stay. Subsequent referrals to other care settings (death, home, home care, hospice, oncology) and changes in the pathway of the oncologic treatment (on/off, uncertain) were assessed at the time of discharge. Patients or their relatives were contacted by phone 1 month after discharge, to collect information on the care setting, the use of anticancer therapies, or to know if the patient died. Patients were considered to be depressed and anxious when they reported moderate-severe intensity on ESAS ($\geq 4/10$) [21, 22].

Statistical analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. Continuous data are expressed as mean ± SD, unless otherwise specified. Differences between groups were assessed by the chi-square test or the Fisher exact test, as needed for categorical variables, and by the independent Student *t* test for continuous parameters. The univariate analysis of variance (ANOVA) was performed for parametric variables with multiple comparisons. The variables significantly related to the patient groups were analyzed in the multivariate logistic regression model to examine the correlation between patient characteristics (independent variables) and patient groups (dependent variable). Effect sizes were used to express the mean score differences between patient subgroups in relation to the standard deviations. Data were analyzed by IBM SPSS Software 22 version (IBM Corp., Armonk, NY, USA). All p values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Three hundred-fourteen consecutive cancer patients admitted to the APSCU were surveyed. The characteristics in patients with and without anxiety and depression are reported in Table 1. Karnofsky level and age were associated with depression, while females were more likely to be anxious. Patients

Table 1 Characteristics in patients with and without anxiety (AN) and depression (DE)

Patients	Without AN	With AN	*P**	Without DE	With DE	*P**
Age (years, mean SD)	65.6 (12.4)	65.0 (10.9)	0.698	63.7 (12.2)	67.2 (11.1)	0.014
Gender M/F	112/62	58/62	0.008	90/63	80/61	0.725
Karnofsky (mean SD)	47.2 (11.0)	45.9 (10.3)	0.315	48.5 (11.7)	44.8 (9.2)	0.004
Primary tumor						
Lung	33	29	0.009	29	33	0.012
Breast	27	18		23	22	
Genitourinary	25	19		21	23	
Gastrointestinal	24	21		26	19	
Liver	17	1		14	4	
Pancreas	4	11		2	13	
Head-neck	8	4		6	6	
Unknown	10	2		10	2	
Hematologic	13	10		14	9	
Other	13	5		8	10	
Stage of disease						
Locally advanced	22	23	0.140	20	25	0.331
Metastatic	136	87	0.271	117	105	0.683
No evidence of disease	16	10	0.689	16	11	0.545
People living with the patients						
Alone	15	11	0.993	11	15	0.601
Partner	70	47		60	57	
Partner and/or sons/daughters	87	61		81	67	
Nursing home	2	1		1	2	
Presence of caregiver	152	96	0.224	132	116	1.0
Education						
No school	8	2	0.543	6	4	0.242
Primary	61	27		53	45	
Secondary school	51	40		29	52	
High level	21	26		25	22	
Degree	23	15		20	18	
Disease awareness, patient						
Complete	94	63	0.135	91	66	0.095
Partial	63	52		52	63	
Absent	17	5		10	12	
Disease awareness, caregiver						
Complete	143	106	0.259	126	123	0.510
Partial	25	11		22	14	
Absent	6	3		5	4	
Admission						
Planned admission	138	92	0.199	113	117	0.164
Unplanned admission (emergency)	26	25		32	19	
Transfer from other units	10	3		8	5	
Readmissions						
Indications for admission						
Uncontrolled pain opioid-related	120	100	0.006	108	112	0.106
Toxicity	28	19	0.231	25	22	0.186
Anticancer toxicity	33	23	1.0	26	30	0.375
Other symptoms	98	72	0.550	75	95	0.002
End-of-life care	12	10	0.658	6	16	0.025
Proposal for referral						

Table 1 (continued)

Patients	Without AN	With AN	*P**	Without DE	With DE	*P**
GP	1	3	0.407	2	2	0.940
Oncologist	113	67		95	85	
PSCU follow-up	3	2		1	4	
Other hospital physicians	26	16		23	19	
Home palliative care physicians	10	14		12	12	
Family/caregiver	14	11		13	12	
Other	7	7		7	6	
Treatments in the previous 30 days						
Chemotherapy	51	38	0.077	46	43	0.637
Chemotherapy + target therapy	3	5		3	5	
Chemotherapy + radiotherapy	2	1		2	1	
Target	14	2		12	4	
Radiotherapy therapy	4	2		4	2	
Hormonal therapy	10	2		5	7	
Hormonal + target	2	0		1	1	
Therapy						
None	88	70		80	78	
Surgery	15	14	0.429	19	10	0.170
Length of stay	6.7 (4.5)	7.7 (8.6)	0.239	6.8 (4.6)	7.5 (8.1)	0.345
OME	105 (171)	142 (157)	0.136	110 (153)	132 (176)	0.363

OME Oral morphine equivalents

*Chi-square test or Fisher exact test, as needed for categorical variables; independent Student *t* test for continuous parameters; univariate analysis of variance (ANOVA) for parametric variables with multiple comparisons

with pancreatic cancer presented more psychological distress, while patients with liver cancer presented the opposite data. Patients admitted for uncontrolled pain were more likely to be anxious, while patients admitted for other symptoms or end-of-life care were more likely to be depressed. No other statistical differences were found in other parameters taken into consideration. Eighty-six and 66 patients improved their level of depression and anxiety, respectively (passing from ≥ 4 to 0–3, from T0 to T7), after that palliative care intervention resulted in a significant improvement of the other symptoms. Changes were statistically significant for both symptoms ($P < 0.0005$). The presence of anxiety and depression (≥ 4/10 on ESAS) was significantly associated with a higher level of symptom expression at admission (Table 2). This finding was also reported at T7 (Table 3).

In patients presenting both psychological symptoms, symptom expression was significantly more relevant in comparison with patients not reporting moderate-severe psychological symptoms (Table 4). Expressed in terms of effect sizes, all *d* values evaluated for global ESAS mean score differences between patient subgroups were between 1.08 and 2.36. The multivariate analysis of significant variables at T0 regarding anxiety is reported in Table 5. Pain and depression were independently associated with anxiety at T0. The multivariate analysis regarding depression is reported in Table 6. Variables independently associated with depression were drowsiness, appetite, and anxiety at T0.

Discussion

As reported in previous studies [17, 23], palliative care intervention was able to decrease the intensity of both psychological and physical symptoms. The findings of this study also suggest that anxiety and depression may affect the expression of most symptoms included in the ESAS, which is one the most common instrument to measure symptom intensity and eventual changes after a palliative care intervention. Specifically, pain was highly expressed in patients with anxiety, while depression more likely occurred in patients with drowsiness and poor appetite. Of interest, psychological symptoms were inevitably associated between them. Thus, anxiety and depression differently affect some symptoms. While pain and anxiety may directionally influence each other [23], depression may arise as a final common pathway of distress and physical suffering [2]. Even after a palliative care intervention able to produce a significant decrease in intensity of ESAS symptoms, anxiety and depression were still associated with symptom hyper-expression, underlining that this

Table 2 ESAS values at T0 in patients with and without anxiety (anx) and in patients with or without depression (dep)

Symptoms	Without anx 174 points	With anx 120 points	P*	Without dep 153 point	With dep 141 points	P*
Drowsiness	4.1 (2.6)	4.8 (3.1)	0.047	3.7 (2.7)	5.1 (2.8)	< 0.0005
Weakness	5.4 (2.9)	6.4 (2.6)	0.003	5.5 (2.8)	6.1 (2.8)	0.084
Nausea	1.8 (2.6)	2.6 (3.2)	0.013	1.9 (2.7)	2.2 (2.9)	0.419
Pain	4.6 (2.9)	6.2 (2.5)	< 0.0005	4.9 (2.9)	5.6 (2.8)	0.034
Dyspnea	1.8 (2.8)	3.4 (3.5)	< 0.0005	2.1 (2.9)	2.8 (3.4)	0.044
Anxiety	0.8 (1.2)	6.5 (1.8)	–	1.9 (2.5)	4.4 (3.3)	< 0.0005
Depression	2.2 (2.5)	4.9 (3.1)	< 0.0005	0.7 (1.2)	6.1 (1.9)	–
Insomnia	4.1 (3.1)	5.3 (3.4)	0.002	4.3 (3.4)	4.9 (3.2)	0.127
Appetite	4.1 (3.1)	5.6 (3.2)	< 0.0005	3.9 (3.1)	5.7 (3.1)	< 0.0005
Poor well-being	5.4 (2.3)	6.8 (2.2)	< 0.0005	5.4 (2.4)	6.5 (2.1)	< 0.0005
Global ESAS	33.9 (12.5)	52.1 (14.3)	< 0.0005 effect size $d = 1.35$	34.1 (13.6)	49.3 (14.5)	< 0.0005 effect size $d = 1.08$

*Univariate analysis of variance (ANOVA)

group of patients may be disadvantaged in terms of symptom control.

Data in literature are controversial, also because of the different methodologies and tools used. Available depression measures have strengths and limitations [24]. In patients attending a palliative care day unit, a close association between physical symptoms, including pain and fatigue, quality of life, and mobility, and the presence of depression has been found [1]. Significant pain was strongly and independently associated with emotional distress [8].

In a retrospective study, patients with depressive mood and anxiety expressed higher frequency of symptoms with an intensity of > 1, with a varied intensity. This analysis included ESAS symptoms with no zero intensity and was performed on baseline data [8]. In a large sample of advanced cancer patients, depression was independently associated with a range of somatic symptoms. However, only the sum of ESAS was considered. Moreover, only one point assessment was taken into consideration, due to the cross-sectional design, which avoids to draw conclusions on directionality [14]. Similarly, in a study performed in a hospice, depressed mood and dyspnea were independent predictors for anxiety [25]. In a secondary cross-sectional analysis, anxiety and depression presented strong and independent associations with mental health domains and somatic symptom burden in cancer patients. However, depression had a more pervasive association with multiple other domains of health-related quality of life [26]. Similarly, in a cross-sectional secondary analysis, depression severity significantly correlated with a number of physical symptoms, symptom distress, and symptom severity, independently of cancer type, functional status, chemotherapy status, and survival time [12]. Finally, psychological distress has

Table 3 ESAS values at T7 in patients with and without anxiety (anx) and in patients with or without depression (dep)

Symptoms	Without anx 206 points	With anx 59 points	P*	Without dep 208 points	With dep 57 points	P*
Drowsiness	2.5 (2.5)	4.0 (2.5)	< 0.0005	2.4 (2.5)	4.4 (2.4)	< 0.0005
Weakness	2.7 (2.4)	5.1 (2.7)	< 0.0005	2.9 (2.6)	4.8 (2.3)	< 0.0005
Nausea	0.8 (1.3)	1.3 (2.4)	0.059	0.7 (1.6)	1.6 (2.5)	0.001
Pain	2.3 (1.9)	3.5 (2.2)	< 0.0005	2.3 (1.8)	3.6 (2.3)	< 0.0005
Dyspnea	1.0 (1.9)	2.2 (2.8)	< 0.0005	1.1 (2.1)	1.8 (2.6)	0.038
Anxiety	0.6 (1.1)	5.4 (1.6)	–	1.0 (1.7)	4.1 (2.7)	< 0.0005
Depression	1.1 (1.6)	3.8 (2.7)	< 0.0005	0.7 (1.1)	5.2 (1.5)	–
Insomnia	2.2 (2.6)	4.1 (2.9)	< 0.0005	2.3 (2.7)	3.9 (2.9)	< 0.0005
Appetite	2.5 (2.5)	4.4 (3.1)	< 0.0005	2.7 (2.6)	4.0 (2.9)	0.001
Poor well-being	3.3 (2.1)	4.8 (2.2)	< 0.0005	3.3 (2.2)	4.9 (2.1)	< 0.0005
Global ESAS	19.2 (11.4)	38.5 (14.2)	< 0.0005 effect size $d = 1.49$	19.4 (11.5)	38.4 (14.2)	< 0.0005 effect size $d = 1.48$

*Univariate analysis of variance (ANOVA)

Table 4 ESAS values in patients with and without both anxiety (anx) and depression (dep) at T0 and T7

Symptoms	T0				T7			
	All*	Without anx and dep	With anx and dep	P^	All*	Without anx and dep	With anx and dep	P^
Drowsiness	4.18 (2.7)	3.7 (2.5)	5.2 (2.9)	< 0.0005	2.86 (2.6)	2.4 (2.5)	4.9 (2.3)	< 0.0005
Weakness	5.64 (2.8)	5.3 (2.9)	6.4 (2.7)	0.006	3.27 (2.7)	2.7 (2.5)	5.6 (2.2)	< 0.0005
Nausea	1.96 (2.7)	1.8 (2.6)	2.6 (3.2)	0.049	0.90 (1.9)	0.8 (1.7)	2.0 (2.8)	< 0.0005
Pain	5.25 (2.8-3)	4.6 (2.9)	6.2 (2.6)	< 0.0005	2.59 (2)	2.2 (1.8)	3.8 (2.4)	< 0.0005
Dyspnea	2.34 (3.1)	1.6 (2.6)	3.3 (3.5)	< 0.0005	1.34 (2.25)	1.1 (2.0)	2.5 (2.9)	< 0.0005
Anxiety	2.94 (3.1)	0.7 (1.2)	6.7 (1.8)	–	1.68 (2.3)	0.6 (1.0)	5.8 (1.6)	–
Depression	3.15 (2)	0.7 (1.2)	6.6 (1.9)	–	2.85 (2.2)	0.7 (1.1)	5.6 (1.7)	–
Insomnia	4.44 (3.2)	3.9 (3.3)	5.2 (3.4)	0.007	2.34 (2.8)	2.2 (2.7)	4.9 (2.8)	< 0.0005
Appetite	5.88 (2.3)	3.5 (2.9)	5.8 (3.1)	< 0.0005	2.92 (2.7)	2.5 (2.4)	4.8 (2.7)	< 0.0005
Poor well--being	5.7 (2.3)	5.0 (2.4)	6.8 (2.2)	< 0.0005	3.60 (2.2)	3.2 (2.2)	5.3 (2.3)	< 0.0005
Global ESAS	38.79	30.7 (12.4)	54.5 (14.7)	< 0.0005 effect size $d = 1.75$	20.01 (15.7)	18.2 (11.0)	45.0 (11.7)	< 0.0005 effect size $d = 2.36$

*All = $P < 0.001$

^ Univariate analysis of variance (ANOVA)

been reported to be responsible of prolonged hospitalization [27]. However, this finding was not confirmed in the present study, as differences in hospital admission were not significant. Most of these studies lack a longitudinal observation, having in general a cross-sectional design without a second point assessment to evaluate possible changes in physical and psychological symptoms and their relationship. Considering that the cut-off for a diagnosis of depression and anxiety in the ESAS still remains controversial, we have chosen the level of ≥ 4, based on recent observation suggesting that the personal targets may serve as a guide to find what is acceptable for patients. In recent papers assessing the personalized symptom goal, most patients admitted to a palliative care unit had a target value of ≤ 3 for all ESAS items, including anxiety and depression [19, 28]. Thus, it is likely that values of 4 or more are more consistent with what the patients consider a mean non-desirable level of intensity. On the other hand, in a previous study, ESAS anxiety or depression scores > 3 detected quite well the severe depression diagnoses with HADS (Hamilton Anxiety and Depression Score, sensibility = 75, specificity = 84; sensibility = 87, specificity = 90, respectively) [22]. Such threshold was used to report moderate-severe psychological symptoms in a previous study [21].

Table 5 Multiple regression analysis of significant variables at T0 for anxiety

Anxiety T0[a]	Exp (B)	95% CI Exp (B)	P
Pain T0	1.229	1.10–1.37	< 0.0005
Weakness T0	1.037	0.92–1.16	0.545
Nausea T0	1.065	0.96–1.18	0.229
Depression T0	1.386	1.24–1.54	< 0.0005
Drowsiness T0	0.931	0.83–1.04	0.223
DyspneaT0	1.063	0.96–1.18	0.238
Insomnia T0	1.074	0.97–1.18	0.143
Appetite T0	1.049	0.94–1.16	0.359
Poor well-being T0	1.100	0.94–1.28	0.228

[a] The reference category is 0

Table 6 Multiple regression analysis of significant variables at T0 for depression

Depression at T0[a]	Exp (B)	95% CI Exp (B)	P
Pain T0	0.990	0.90–1.09	0.840
Drowsiness T0	1.152	1.04–1.28	0.007
Dyspnea T0	0.973	0.89–1.06	0.554
Appetite T0	1.118	1.02–1.23	0.022
Poor well-being T0	1.065	0.93–1.22	0.367
Anxiety T0	1.314	1.19–1.45	< 0.0005

[a] The reference category is 0

A limitation of this study is represented by the lack of structured interviews according to DSM-IV to diagnose anxiety and depression, or other instruments such as HDAS. HADS, however, was found to be accurate as an indicator of depression and anxiety and resulted to be significantly associated with anxiety and depression measured with ESAS [8]. On the other hand, a high specificity (> 90%) for major depression with ESAS has been found—depression cut-offs of 6 or greater, highlighting the utility of this tool to support the diagnosis of major depression. The choice of a cut-off of 4 or more could be more specific, either for anxiety or depression, as well as other ESAS symptoms. Most of ESAS symptoms have been found to have a mean personalized target of 3 or less; thus, an intensity of 4 or more may be an acceptable level reflecting for individuals what it means for patients, trespassing that threshold [19]. We lack information about patients who were not able to participate because they are severely ill. The number of these patients in an ASPCU, however, is negligible, the mortality being about 3%. The use of antidepressants or benzodiazepines for anxiety was not taken into consideration. Again, the data presented in this study reflects what commonly occurs in patients admitted to an ASPCU from admission to discharge or 7 days after (this interval includes 90% of admission staying). On the other hand, this interval cannot provide an effective evaluation of antidepressant drugs, which have a late onset. Finally, as this is an exploratory study, from these findings, it is not possible to make reliable interpretations, and data should be better evaluated in confirmatory studies.

Conclusion

Psychological symptoms of ESAS concur to hyper-express some symptoms and make symptom control more difficult. A clear association between anxiety and depression exists. Pain is over-expressed in patients with anxiety, while poor appetite and drowsiness have higher intensity in patients with depressed mood. Further studies with appropriate design should be performed to explore the direction of such relationships. Moreover, the role of psychological symptoms should be evaluated in other care settings, hospice, or home care, in which patients are admitted in a more advanced stage of disease.

Compliance with ethical standards

The study was approved by the ethical committee and informed consent was obtained.

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Lloyd-Williams M, Shiels C, Taylor F, Dennis M (2009) Depression–an independent predictor of early death in patients with advanced cancer. J Affect Disord 113:127–132
2. Lo C, Zimmermann C, Rydall A, Walsh A, Jones JM, Moore MJ, Shepherd FA, Gagliese L, Rodin G (2010) Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J Clin Oncol 28:3084–3089
3. Cheung WY, Barmala N, Zarinehbaf S, Rodin G, le LW, Zimmermann C (2009) The association of physical and psychological symptom burden with time to death among palliative cancer outpatients. J Pain Symptom Manag 37:297–304
4. Ciaramella A, Poli P (2001) Assessment of depression among cancer patients: the role of pain, cancer type and treatment. Psychooncology 10:156–165
5. Chochinov HM, Wilson KG, Enns M, Lander S (1997) "Are you depressed?" screening for depression in the terminally ill. Am J Psychiatry 154:674–676
6. Katon W, Lin EHB, Kroenke K (2007) The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 29:147–155
7. Kroenke K, Rosmalen JGM (2006) Symptoms, syndromes, and the value of psychiatric diagnostics in patients who have functional somatic disorders. Med Clin North Am 90:603–626
8. O'Connor M, Weir J, Butcher I et al (2012) Pain in patients attending a specialist cancer service: prevalence and association with emotional distress. J Pain Symptom Manag 43:29–38
9. Brown LF, Kroenke K (2009) Cancer-related fatigue and its associations with depression and anxiety: a systematic review. Psychosomatics 50:440–447
10. Zaza C, Baine N (2002) Cancer pain and psychosocial factors:a critical review of the literature. J Pain Symptom Manag 24:526–542
11. Wasteson E, Brenne E, Higginson IJ, Hotopf M, Lloyd-Williams M, Kaasa S, Loge JH, the European Palliative Care Research Collaborative (EPCRC) (2009) Depression assessment and classification in palliative cancer patients: a systematic literature review. Palliat Med 23:739–753
12. Fitzgerald P, Lo C, Li M, Gagliese L, Zimmermann C, Rodin G (2015) The relationship between depression and physical symptom burden in advanced cancer. BMJ Support Palliat Care 5:381–388
13. Teunissen SCCM, de Graeff A, Voest EE, de Haes JCJM (2007) Are anxiety and depressed mood related to physical symptom burden? A study in hospitalized advanced cancer patients. Palliat Med 21:341–346
14. Delgado-Guay M, Parsons HA, Li Z, Palmer JL, Bruera E (2009) Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer 17: 573–579
15. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, Glare P, Nabal M, Viganò A, Larkin P, de Conno F, Hanks G, Kaasa S, Steering Committee of the European Association for Palliative Care (2005) Prognostic factors in advanced cancer patients: evidence-based clinical recommendations-a study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol 23:6240–6248
16. Austin P, Wiley S, McEvoy PM, Archer L (2011) Depression and anxiety in palliative care inpatients compared with those receiving palliative care at home. Palliat Support Care 9:393–400
17. Mercadante S, Adile C, Caruselli A, Ferrera P, Costanzi A, Marchetti P, Casuccio A (2016) The palliative-supportive care unit

in a Comprehensive Cancer Center as crossroad for patients' oncological pathway. PLoS One 11:e0157300
18. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K (1991) The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 7:6–9
19. Hui D, Bruera E (2017) The Edmonton Symptom Assessment Scale remains useful for depression screening. Palliat Med 31: 483–484
20. Chang VT, Hwang SS, Feuerman M (2000) Validation of the Edmonton Symptom Assessment Scale. Cancer 88:2164–2171
21. Rhondali W, Yennurajalingam S, Ferrer J, Chisholm G, Filbet M, Bruera E (2014) Association between supportive care interventions and patient self-reported depression among advanced cancer outpatients. Support Care Cancer 22:871–879
22. Ripamonti CI, Bandieri E, Pessi MA, Maruelli A, Buonaccorso L, Miccinesi G (2014) The Edmonton Symptom Assessment System (ESAS) as a screening tool for depression and anxiety in non-advanced patients with solid or haematological malignancies on cure or follow-up. Support Care Cancer 22:783–793
23. Modonesi C, Scarpi E, Maltoni M, Derni S, Fabbri L, Martini F, Sansoni E, Amadori D (2005) Impact of palliative care unit admission on symptom control evaluated by the Edmonton Symptom Assessment System. J Pain Symptom Manag 30:367–373
24. Wakefield CE, Butow PN, Aaronson NA, Hack TF, Hulbert-Williams NJ, Jacobsen PB, International Psycho-Oncology Society Research Committee (2015) Patient-reported depression measures in cancer: a meta-review. Lancet Psychiatry 2: 635–647
25. Grotmol KS, Lie HC, Loge JH, Aass N, Haugen DF, Stone PC, Kaasa S, Hjermstad MJ (2018) Patients with advanced cancer and depression report a significantly higher symptom burden than non-depressed patients. Palliat Support Care 10:1–7. https://doi.org/10.1017/S1478951517001183
26. Zweers D, de Graaf E, de Graeff A et al (2017) The predictive value of symptoms for anxiety in hospice inpatients with advanced cancer. Palliat Support Care 16(5):602–607
27. Brown LF, Kroenke K, Theobald DE, Wu J, Tu W (2010) The association of depression and anxiety with health-related quality of life in cancer patients with depression and/or pain. Psychooncology 19:734–741
28. Nipp RD, El-Jawahri A, Moran SM et al (2017) The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. Cancer 123: 4720–4727