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Abstract

Context: Quality of life (QoL) and depression are important patient-reported outcomes in cancer care. However, the relative importance of depression severity in predicting QoL remains unclear due to few methodologically sound studies.

Objectives: To examine whether depression contributes to impairment of QoL irrespective of prognostic factors and symptom burden.

Methods: 563 patients were included from the European Palliative Care Research Collaborative Study (EPCRC-CSA), an international, multi-centre, cross-sectional study. The relative importance of prognostic factors (systemic inflammation (mGPS), co-morbidities and physical performance (KPS), symptom burden (loss of appetite, breathlessness, nausea (ESAS) and pain (BPI)) and depression severity (PHQ-9) in predicting Global Health/QoL (EORTC-QLQ-C30) were assessed using hierarchical multiple regression models.

Results: 55% were females, median age 64 years, 87% had metastatic disease, median KPS was 70 and mean global QoL 50.5 (SD=23.3). Worse QoL was associated with increased systemic inflammation (mGPS=1 β=-0.12, p=0.003, mGPS=2 β=-0.09, p=0.023), lower physical performance (β=0.17, p<0.001), reduced appetite (β=-0.15, p<0.001), breathlessness (β=-0.11, p=0.004), pain (β=-0.14, p=0.002), and higher depression severity (β=-0.27, p<0.001). The full model accounted for 29% of the observed variance in QoL scores. The strongest predictor was depression severity, accounting for 5.8% of the variance.

Conclusion: Depression severity was the strongest single predictor of poorer QoL in this sample of patients with advanced cancer, after accounting for a wide range of clinically relevant variables. Future studies should investigate the contribution of psychosocial variables on QoL. Our findings emphasize the importance of managing depression to achieve the best possible QoL for these patients.

Key Words: depression, quality of life, advanced cancer, prognosis, population study

Introduction

Quality of life (QoL) is becoming an increasingly important factor in cancer care, and especially so in palliative care. The World Health Organization defines palliative care as "an approach that improves QoL of patients and their families (…) by means of early identification and impeccable assessment and treatment of pain and other problems (…)".[1] As such, best possible QoL is the main goal of palliative care and optimal symptom management the primary means to achieve it. Still, the concept of QoL is not defined by WHO, leaving its content open to interpretation. In line with the 2006 Food and Drug Administration Guideline, we define QoL as "a general concept that implies an evaluation of the impact of all aspects of life on general well-being".[2]

The early integration of palliative care services into standard oncology is currently a topical issue as reflected by the American Society of Clinical Oncology's (ASCO) Provisional Clinical Opinion.[3] Evidence suggests that patients with advanced cancer benefit in terms of improved symptom management and enhanced QoL when receiving early palliative care.[4] With the increased focus on the early integration of palliative care into oncology, knowledge of what contributes to good QoL among patients with advanced cancer is important in oncology and palliative care. Such knowledge aids the early identification of those at risk of poorer QoL, and is useful for informing practice and supporting the development of targeted interventions.

Some studies have identified determinants of QoL in patients with advanced cancer. However, these were often performed in quite restricted samples (among patients at the very end of life) or after specific treatments (response to radiation therapy for painful bone metastases).[5] The literature suggests some predictive factors to apply across the disease trajectory. Patients with advanced cancer generally experience multiple symptoms and decreasing function as the disease progresses[6], and associations have been reported between poorer QoL and both somatic symptoms and decreased physical functioning.[7] Other prognostic factors, such as weight loss and comorbidities, are also reported to predict QoL.[7-10] Systemic inflammation, measured by the modified Glasgow Prognostic Score (mGPS), is another prognostic factor associated with QoL.[11] A recent study found physical functioning and increasing systemic inflammation to be associated with worsening of QoL independently of each other.[9]

Depressive disorders in patients with advanced cancer is common and have an average prevalence rate of around 15% based on structured clinical interviews or patient-reported measures that include the diagnostic criteria of a depressive disorder.[12,13] Depression is associated with reduced functional status, lower treatment compliance, prolonged hospitalizations and a greater likelihood for a desire for hastened death.[14,15] Not only does it affect the intensity of physical symptoms, but the presence of depression also complicates symptom management.[16] Depression in patients with advanced cancer is often unrecognized in the clinic, hampering adequate treatment.[17]

In the general population, depression is consistently found to be a strong predictor of impaired QoL.[18] We identified very few studies that rigorously investigated this issue in people with advanced disease. Firstly, the measurement of depression in patients with cancer is challenging, due to the overlap of somatic symptoms of depression and progressive cancer. Depression is often assessed by the Hospital Anxiety and Depression Scale (HADS),[10] but importantly, a review of the HADS as a screening tool of major depression reported a widely varying diagnostic accuracy in people with a variety of cancers, in line with other studies in patients with advanced cancer.[19] Further, as disease progression is associated with worsening QoL, this should be considered when investigating determinants of QoL, yet often disease severity was only assessed by functional performance, if it was considered at all.[20]

Due to the methodological shortcomings of the studies to date, it remains unclear whether depression is contributing to impaired QoL in patients with advanced cancer *irrespective of* symptom burden and other prognostic factors. The aim of the present study, which includes a range of relevant disease and treatment variables, is to examine whether depression contributes to impairment of QoL. It is hypothesized that patients with a poorer prognosis, higher symptom burden and higher depression severity also report poorer quality of life than patients with better prognosis, and lower symptom burden and depression levels. Moreover, we will explore the relative importance of depression severity in predicting QoL in patients with advanced cancer.

Methods

Study design and patients

Data were analysed from a large international cross-sectional study, the EPCRC-CSA (www.epcrc.org), aiming to improve classification and assessment of symptoms in palliative care.[21] Patients with advanced cancer were recruited from 17 centers in eight countries in 2008 and 2009, including in- and out-patient units, hospices/inpatient palliative care beds, general oncology and medical wards. Potentially eligible participants were people with: incurable metastatic or locally advanced disease; and age 18 years or above. Exclusion criteria were: inability to complete the assessment because of language problems, physical incapacity or obvious cognitive impairment according to standard clinical criteria. Overall, a convenience sample of 1051 eligible participants was recruited.[21] Of these, 12 patients with severe cognitive impairment (Mini-Mental State Exam (MMSE) sum-score<18)[22] were excluded. A further 476 patients were missing one or more of the variables of interest in this study and for which a value could not be imputed (biomarkers and/or QoL). These patients were therefore excluded. The final sample consisted of 563 (53.6%) patients with advanced cancer, all with complete datasets.

Study measurements

Health care personnel collected socio-demographic and medical data, while participants completed a range of patient-reported instruments. Data collection was done directly on touch-sensitive tablet computers.[23]

QoL. The Global Health/QoL scale consists of two items evaluating overall health ("How would you rate your overall health during the past week?) and QoL ("How would you rate your overall quality of life during the past week") scored on 8-point numerical rating scales with 0 being *"very poor"* and 7 being "*excellent".* The scores are transformed to a 0-100 score, according the EORTC manual,[24] and a higher score indicates better Global Health/QoL. This measure has proven useful and reliable for assessment of patients' self-perceived overall QoL as documented in a recent review[25] and showed good internal consistency in our sample (Cronbach's α= 0.83).

Medical status: Medical status was assessed based on primary cancer diagnosis (breast cancer, pulmonary cancer, gastrointestinal cancer, male genital cancers and all others), and current disease status: loco-regionally advanced or metastatic disease (Table 1).

Current treatment: Current treatment assessed whether the patients were receiving opioids (yes/no), or any oncological treatment: chemotherapy only, other oncological treatment (radiotherapy with or without chemotherapy, hormone therapy and/or other anti-tumour treatment) or no oncological treatment.

Prognostic factors. Medical information was retrieved from patient records and health care professionals (HCP) registrations. The latter included evaluation of the patients' performance status by the Karnofsky Performance Status (KPS);[26] registration of co-morbidities (heart disease, arthritis, COPD, renal, liver disease and "others"). The biomarkers albumin and CRP were either extracted from the patient's medical record, if samples were collected within three days of study-inclusion, or from blood samples collected by HCPs and analysed according to local procedures. As a measure of systemic inflammation, the biomarkers were combined to calculate the modified Glasgow Prognostic Score (mGPS): 0=CRP≤10 mg/L; 1= CRP>10mg/L; and 2= CRP>10mg/L and albumin<35g/L.[27] Self-reported weight change over the last six months was also included as a prognostic factor (self-reported weight six months ago minus current self-reported weight).

Symptom burden: "Symptom burden" was measured using three somatic symptoms from the Edmonton Symptom Assessment Scale (ESAS)[28]; nausea, lack of appetite and breathlessness. Pain was measured by one question from the Brief Pain Inventory (BPI)[29]; "pain at its worst during the last 24 hours". The ESAS and BPI items were all scored on 11-point numerical rating scales with 0 as "*no symptom at all"* and 10 is "*worst possible symptom*". Thus, ESAS items on psychological symptoms, pain and general well-being/QoL were not included in the analyses due to content overlap with depression and overall QoL.

Depressive symptom severity: Depressive symptoms were assessed using the PHQ-9, a self-report questionnaire commonly used in medically ill samples, including patients with cancer.[13,30] The PHQ-9 items correspond to the DSM-5 diagnostic criteria for major depressive disorder (MDD) and assess the frequency at which they have been bothersome during the past two weeks: 0="*not at all*", 1="*several days*", 2="*more than half the days*" and 3="*nearly every day*". Symptom severity, however, is measured by summing the scores on all nine items.[31,32] We have previously shown in this sample that the total score is likely conflated by high

scores on somatic symptoms of depression that commonly overlap with symptoms of advanced cancer disease.[13] To avoid artificial inflation of any relationships between depressive symptoms severity and QoL in this study, we excluded the somatic PHQ-9 items and summed the scores on the five non-somatic items (depressed mood, anhedonia, feeling of worthlessness, poor concentration and thoughts about death/self-harm). Scores ranged from 0-18, with a higher score indicating higher depression symptom severity. The PHQ-9 showed acceptable internal consistency in our sample (Cronbach's α= 0.79).

Statistical methods

Chi-square, independent group t-tests and Mann-Whitney U tests were used to compare differences between groups of patients included and not included in the study. Variables to be included in the multivariate models were determined using bivariate regression models with statistical significance set at $p<0.10$. Candidate variables were: medical status variables; current treatment variables; prognostic factors; symptom burden variables; and depression. Demographic variables were controlled for in the multivariate models. Multivariate, hierarchical regression was used to explore the relationships between the above-mentioned variables and QoL. This method allowed us to estimate the unique variance accounted for in the QoL scores by the groups of variables. *P*-values<0.05 were considered statistically significant. Statistical analyses were done using IBM-SPSS 22 (Armonk, NY: IBM Corp.).

Ethical considerations

The study was performed according to the Helsinki declaration. Ethical approval was obtained at each site before study start. All participants gave their written informed consent.

Results

Sample characteristics

Sample characteristics and comparisons between those included (n=563) or not (n=488) in the sample are provided in Table 1. In brief, those included in the study were significantly more likely to be female ($p=0.013$); Norwegian ($p<0.001$); to have gastrointestinal cancer; but less likely to have breast cancer ($p<0.001$); to be in-patients ($p<0.001$); to have metastatic disease ($p=0.017$); to receive oncological

treatments (p<0.001) or opioids (p<0.001); than those not included (p<0.020). Also, the included patients had significantly higher physical functioning scores (KPS, p<0.001), lower CRP (p=0.001), higher albumin (p=*0.008),* lower worst pain (p<0.001) and lower depression severity scores (p<0.001, Table 1). There were no significant differences in QoL scores, age, marital status and cognitive functioning scores (MMSE) between those included and not included. Moreover, about two-thirds of the patients were in-patient and one-third were out-patients. However, a patient's in- or out-patient status did not reflect the stages of disease due to organizational issues at the different centers and is therefore not included in our analyses.

Associations with QoL

Univariate models. The univariate models are presented in Table 2. The demographic variables age, gender and marital status were not associated with QoL scores. The following variables were significantly associated with a lower QoL score: a primary diagnosis of gastrointestinal cancer; receiving chemotherapy only; not receiving opioids; factors indicating poor prognosis (a higher mGPS score, lower KPS score, weight loss in the last 6 months); and increased symptom burden (more nausea and pain, appetite loss and breathlessness, and increased depression severity.)

Multivariate hierarchical model. In the final multivariate model, higher mGPS, lower KPS, loss of appetite and more breathlessness and pain, and higher depression severity were significantly associated with lower Global Health/QoL scores (Table 2). The demographic variables entered in Block 1 were not significantly associated with QoL. Medical status variables entered in Block 2 and current treatment variables entered in Block 3 accounted for 0.05% (p=0.134) and 6.9% (p<0.001) of the variance in QoL scores respectively. Combined, the prognostic factors entered in Block 4 accounted for 7.9% (p<0.001) of the observed variance in QoL scores over and above the variables entered in Blocks 1-3. Symptom burden variables, entered in Block 5, accounted for 9.3% (p<0.001) of the variance in QoL over and above the above-mentioned variables. Increased depression severity, entered in Block 6, was the strongest single predictor of QoL scores in the model, accounting for 5.8% (p<0.001) of the variance in QoL scores over and above that accounted for by all of the other variables. The full model accounted for 29% (adjusted R^2) of the observed

variance in QoL scores. For comparison, we re-ran the model using the total score of all nine depression symptoms, including the four somatic symptoms. In this model, depression symptom severity accounted for 7.1% of the unique variance of the QoL scores.

Lastly, to investigate how much variance each of the significant predictors explained of the QoL scores whilst controlling for all other variables, including depression, we ran five separate multiple hierarchical regression models. For each of the five models we included in Block 1 all variables but the significant predictor of interest, which was included in Block 2. These analyses showed that mGPS explained 1.3% (p=0.006), KPS 2.0% (p<0.001), loss of appetite 1.6% (*p*<0.001), breathlessness 1.0% (*p*=0.004) and worst pain intensity 1.3% (*p*=0.002) respectively of the variance in QoL over and above that explained by all other variables combined.

Discussion

To our knowledge the present study is the first to tease apart the relative importance of treatment related variables, prognostic factors, symptom burden and depression to better understand QoL in patients with advanced cancer. The main finding was the strong association between depression severity and QoL scores. The model explained 29% of the variance in QoL. Depression was the single strongest predictor variable in the model, explaining 5.8% of the variance in the QoL scores.

Depression is prevalent among people with advanced cancer[12] and compromises QoL[10]. Although treatable[33], it is well documented that both doctors and nurses fail to detect emotional distress and patients themselves rarely disclose unless asked.[17] Further, anti-depressive medications are often started too late to have a benefit.[34] Given that the main aim of palliative care is to ensure the best possible QoL[1], these results emphasize the clinical importance of detecting and treating depression as early as possible.

Combined, the prognostic factors accounted for 7.6% of the variance in the QoL scores. Both increased systemic inflammation and poorer physical performance status remained significantly associated with poorer QoL in the multivariate models, confirming their importance for QoL in populations with advanced diseases.[7,8] Sociodemographic variables that predict QoL in the general population[35] such as

age, gender, marital status or highest level of education were not associated with QoL scores in our sample. The literature on the importance of sociodemographic variables for QoL among advanced cancer patients is inconclusive. Some studies report no or only minimal effects of demographic variables. For example, Lundh and colleagues found that being married was associated with lower QoL, while Jordhoy and colleagues found no influence from a live-in partner.[8,36] In line with our findings, it seems that the overall influence of sociodemographic characteristics on QoL amongst severely diseased patients is superseded by their disease status.[8]

To avoid artificially conflating the relationship between depression severity and QoL, we used a modified depression measure that included only the emotional and cognitive symptoms of depression. It is therefore hard to compare the reported depression severity and levels of QoL in our sample with those found in the existing literature. However, the prevalence rate for major depression defined according to the DSM-V diagnostic criteria in the present sample was 11%. This is similar to that reported in a meta-analysis of studies diagnosing major depression based on structured clinical interviews (14.3% (95%CI: 11.1 – 17.9).[12] The mean QoL score of 50.5 is comparable to that reported in similar patient groups.[37] The corresponding numbers for the general population are 5-6% and 75, for depression[38] and QoL[39], respectively.

Study strengths and limitations

The study's cross-sectional design prevents us from making claims of causality between the variables. Further, as our model focuses on disease and treatment, psychosocial variables, such as social support which are likely to contribute to QoL were not included. In addition, associations between some variables may be conflated due to the common method of measurement used, i.e. common-method variance. However, excluding the somatic symptoms from our depression measure and including objective indicators of prognosis and observer-rated measures of physical functioning, which is rarely done in research to date, should reduce this problem. Further, due to ethical regulations, we lack information about patients who were not invited or declined participation. Additionally, our sample reported significantly higher KPS scores and lower levels of systemic inflammation, loss of appetite, pain and depression severity than those not included. Thus, the most

severely affected patients are not likely to be included in our sample. In line with this, the depression prevalence reported on a slightly different part of the EPCRC-CSA sample was somewhat greater than the 11% reported here.[13] Further, our measure of depression is based on self-report rather than on a diagnostic interview. Nevertheless, the PHQ-9 corresponds to the criteria used in the gold standard (the SCID-MDD interview) and is recommended as a screening tool for depression by ASCO.[40] Lastly, data were collected during 2008 and 2009. As such, current treatments may potentially produce slightly different symptom profiles than those described in our sample. However, we do not think this would have influenced the results in any way, as the patients had advanced, incurable disease.

Strengths of this study are that it represents a large international sample of patients with advanced cancer. Second, the sample is well characterized on a broad range of clinically relevant variables. The sample's heterogeneity therefore strengthens the generalizability of our observational design. Many studies do not differentiate between signs and symptoms of disease burden, despite the defined distinction between a subjective experience and an objective indicator.[41] Hence, these results add to the literature by suggesting that subjective symptoms and objective indicators of disease burden contribute to impaired QoL.

In this large, well characterized sample of patients with advanced cancer, we found that the depression severity had by far the strongest association with patients' QoL, irrespective of disease factors, prognostic factors and symptom burden. As such, our findings are a reminder of the importance of attending to psychological symptoms plays in the care of advanced cancer patients. There is a need for improvement in our efforts to detect and treat depressive symptoms.

Declaration of conflict of interest. None of the authors have declared any conflict of interest.

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Table 1. Sample characteristics comparing those included in the study n=563 vs those not included, n=488.

	Included (n=563)			**Not included (n= 488)**			Differences between groups[1]
Continuous variables	Median	range	n	Median	Range	N	*p*
Age	63.0	18-89	563	64.0	22-98	488	0.541
MMSE[2]	29.0	18-30	563	29.0	10-30	457	0.571
KPS	70.0	20-100	563	70.0	20-100	475	<0.001
CRP	12.0	1-436	563	25.0	0.8-431	189	0.001
Total number co-mobidities[3]	1.0	0-4	563	1.0	0-6	485	0.555
ESAS: Nausea	0.0	0-10	563	0.0	0-10	462	0.360
ESAS: Loss of appetite	3.0	0-10	563	3.0	0-10	460	0.006
ESAS: Breathlessness	1.0	0-10	563	1.0	0-10	460	0.346
Worst pain intensity[4]	2.0	0-10	563	4.0	0-10	448	<0.001
Depression symptom severity[5]	2.0	0-15	563	3.0	0-15	406	0.004
Global Health status/QoL	50.0	0-100	563	50.0	0-100	404	0.465
	Included		**Not included**				
Categorical variables	N	%	n	%			
Gender							0.013
Female	248	44.0%	261	53.5%			
Male	315	56.0%	227	46.5%			
Nationality							
Norwegian	366	65.0%	154	31.6%			<0.001
Not Norwegian	197	35.0%	343	68.4%			
Marital status:							0.84
Married/de facto	373	66.3%	315	64.9%			
Not married/divorced/single	190	33.7%	170	35.1%			
Setting:							<0.001
In-patient	385	68.4%	213	43.8%			
Out-patient	178	31.6%	273	56.2%			
Primary Cancer Diagnosis:							0.001
Gastrointestinal tract	171	30.4%	103	21.4%			
Pulmonary	100	17.8%	74	15.4%			
Breast	74	13.1%	103	21.4%			
Male genital organs & prostate	59	10.5%	55	11.4%			
Other[6]	159	28.2%	147	30.5%			
Current disease status[7]:							
Metastatic	485	86.1%	402	82.9%			0.017
Loco-regionally advanced	78	13.9%	83	17.1%			
Current treatment:							
Chemotherapy only	265	47.1%	173	35.7%			<0.001
Other oncological treatments[8]	141	25.0%	85	17.5%			
None	157	27.9%	227	46.8%			
Opioids	291	33.5%	314	40.3%			<0.001
mGPS[9]							
0	263	47%	45	-			
1	154	27%	33	-			
2	146	26%	67	-			

Notes. Abbreviations: KPS = Karnofsky performance scale, where 100=normal functioning and 0=dead.

[1]Mann-Whitney U, chi-square and difference in proportions (Z) tests.

[2]MMSE Mini Mental State Exam

[3]Co-morbidities: Heart disease, Arthritis, COPD, renal- and liver disease and other.

[4]Scored on a 0-10 numerical rating scale: 0 = "No pain", 10 = "Pain as bad as you can imagine in the last 24 hrs".

[5]Depression severity = sum score of all non-somatic symptoms (depressed mood, anhedonia, guilt, trouble concentrating and suicidal ideations), range 0-15).

[6] Other cancers includes (included vs not-included%): urinary cancers (6,4 vs 4,9%), skin cancers incl. malignant melanomas (4,6 vs. 3,1%), leukaemia/lymphoma (3,7 vs. 5,7%), secondary/ill-defined malignant tumours (2,8%), malignant connective / soft tissue tumours (2,7 vs. 3,9%), head and neck (2,5 vs. 3,5%), gynaecological (2,1 vs. 4,1%), tumours of the CNS (1,8 vs. 1,0%), malignant endocrine tumours (1,1 vs. 0,6%), multiple primary cancers (0,2 vs. 1,0%)), malignant bone tumours (0,4 vs. 0,2%).

[7] Metastatic disease includes one or more metastases in the following locations; bone, brain, liver, lung, lymph node, or other.[21]

[8] Other oncological treatments include: radiotherapy without or with chemotherapy, hormone therapy and/or other anti-tumour treatments

[9] mGPS scores were not compared between those included and not due to large number of missing values for those not included.

Table 2. Univariate and hierarchical multivariate regression models predicting Global Health/ QoL. Only univariate predictors (except demographic characteristics) with $p<0.10$ are included in the multivariate regression model. Standardised beta values are shown. Significance levels are indicated as explained below. Reference categories are provided in the notes.

	Univarite	Multivariate					
Model Steps		**1**	**2**	**3**	**4**	**5**	**6**
1 **Demographics**:							
Gender[1]	-0.02	-0,04	-0,03	-0,02	-0,03	-0,05	-0,02
Age[2]	0.06	0,05	0,05	0,08	0,08	0,05	0,04
Maritalstatus[3]	0.01	0,02	0,02	0,05	0,05	0,03	0,03
2 **Medical Status:**							
Diagnosis[4]							
BC vs all others	0.07		0,09	0,06	0,04	0,06	0,04
Pulm. vs all others	0.04		0,04	0,03	0,04	0,10*	0,07
GI vs all others	0.12*		0,12*	0,07	0,08	0,10*	0,08
Male gen. vs all others	0.07		0,07	0,09	0,09	0,09	0,06
Total comorbidities	-0.04		-	-	-	-	-
3 **Current treatment:**[5]							
Chemo only	0.20***			0,18**	0,09	0,07	0,07
Other oncol. treat.	0.01			0,05	0,06	0,03	0,05
Opioides	-0.25***			-0,18***	-0,09*	0,00	0,01
4 **Prognostic factors:**[6]							
mGPS 1	-0,17***				-0,15***	-0,12**	-0,12**
mGPS 2	-0,25***				-0,16***	-0,11**	-0,09*
KPS	0.29***				0.23***	0,18***	0,17***
Weight change	0.09*				0,02	-0,02	-0,03
5 **Symptom Burden:**[7]							
Nausea	-0.16***					0,00	0,03
Loss of appetite	-0.32***					-0,18***	-0,15**
Breathlessness	-0.21***					-0,13**	-0,11**
Worst pain intensity	-0.33**					-0,18***	-0,14**
6 Depression severity[9]	-0.41***						-0.27***
$R^2_{adj.}$		**-0.001**	**0.005**	**0.069**	**0.142**	**0.232**	**0.290**

Note. Significance levels indicated by: *<0.05, **<0.01, ***<0.001.

[1]Male (vs female);

[2]Age categorised in decades: 18-27, 28-37, 38-47, 48-57, 58-67, 68-77, 78-87, 88-100

[3]Married/de facto vs. not married/divorced/single.

[4]Diagnoses: All other diagnoses (vs. Gastro Intestinal cancer (GI), pulmonary cancers (Pulm.), breast cancer (BC), Male genitals (Male gen.))

[5]Current treatments: Chemotherapy vs not receiving chemotherapy, all other treatments vs not receiving treatment or receiving chemotherapy only; opioids (vs. receiving opioids).

[6]Prognostic factors: mGPS - modified Glasgow Prognostic Score, KPS – Karnofsky Performance Status; Weight change: (self-reported weight six months ago) – (current self-reported weight)

[7]Symptom burden: Nausea, loss of appetite and breathlessness were measured by ESAS. Worst pain severity during the last 24 hours by the Brief Pain Inventory. Higher scores indicate higher symptom burden.

[8]Depression severity = sum score of all non-somatic items (depressed mood, anhedonia, guilt, trouble concentrating and suicidal ideations)