Depression - a major contributor to poor quality of life in patients with advanced cancer

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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) was 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) and 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 to 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

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 mean to achieve it. Still, the ambiguous 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”.[1]

The early integration of palliative care services into standard oncology is a topical issue in present oncology, as reflected by the American Society of Clinical Oncology’s (ASCO) Provisional Clinical Opinion.[2] Evidence suggests that patients with advanced cancer benefit in terms of improved symptom management and enhanced QoL when receiving early palliative care.[3] With the increased focus on the early integration of palliative care in oncology, knowledge of what contributes to good QoL among patients with advanced cancer therefore is important in oncology as well as in palliative care. Such knowledge aids the early identification of those at risk of poor QoL, hence informing practice and supporting the development of targeted interventions.

Patients with advanced cancer generally experience multiple symptoms and decreasing functioning as the disease progresses.[4] Yet, only a handful of studies have investigated what contributes to poor QoL among these patients.[5-8] The few studies that have, report associations between somatic symptoms and poorer QoL.[6] Prognostic factors, such as weight loss, comorbidities and physical functioning are also reported to predict QoL.[5,6] Systemic inflammation, measured by the modified Glasgow Prognostic Score (mGPS), is yet another prognostic factor associated with QoL[9]. A recent study found physical functioning and increasing systemic inflammation to be associated with worsening of QoL independently of each other[7].

Depressive disorders in patients with advanced cancer are relatively common, with average prevalence rate estimates of around 15% based on structured clinical

interviews or patient-reported measures that include the diagnostic criteria of a depressive disorder.[10,11] Depression is associated with reduced functional status, lower treatment compliance, prolonged hospitalizations and a greater likelihood for a desire for hastened death.[12,13] Not only does it affect the intensity of physical symptoms, but the presence of depression also complicates symptom management.[14] Nevertheless, depression in patients with advanced cancer is unrecognized in the clinic, clearly hampering adequate treatment.[15]

With regards to studies in advanced cancer patients, the relationship between depression and QoL has mainly been explored in samples of patients at the very end of life.[16,17] In the general population, depression is consistently found to be a strong predictor of impaired quality of life.[18] We identified very few studies investigating this issue among patients with advanced disease earlier in the trajectory,[8] and these were hampered by limitations. Firstly, as disease progression is associated with lowered QoL, this should be properly considered when investigating determinants of QoL, yet disease severity was only assessed by functional performance. Besides, as the measurement of depression in patients with cancer is challenging, primarily due to the overlap of somatic symptoms of depression and progressive cancer, the assessment of depression is crucial. Depression is often assessed by the Hospital Anxiety and Depression Scale (HADS),[8] but importantly, a review of the HADS as a screening tool of major depression reported a widely varying diagnostic accuracy in mixed cancer populations, in line with other studies in patients with advanced cancer.[19]

Due to the methodological shortcomings of the few studies to date, it remains unclear whether depression is associated with, and thus may be contributing to, impairment of quality of life in patients with advanced cancer *irrespective of* symptoms 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 collected for a large international cross-sectional study, the EPCRC-CSA (www.epcrc.org), aiming to improve classification and assessment of symptoms in palliative care were analysed.[20] 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 approached according to the following inclusion criteria: 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] Biomarkers, depression and QoL scores were available for 575 of these patients. For the purpose of the current study, patients with severe cognitive impairment (Mini-Mental State Exam (MMSE) sum-score<18 [22] (n=12), were not included, resulting in a sample 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.[21]

QoL. QoL was measured using the Global Health/QoL sub-scale from the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC-QLQ-C30), one of the most widely used QoL tools in oncology trials.[23] The Global Health/QoL sub-scale consists of two items evaluating overall health and QoL during the past week (range 0-7) that are summed and converted to a 0-100 score. A higher score indicates better QoL. This QoL measure is useful when the aim is to measure the patients' perceived overall QoL[24] 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 HCP registrations. The latter included evaluation of the patients' performance status by the Karnofsky Performance Status (KPS);[25] 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. [26] 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); nausea, lack of appetite and shortness of breath. The items on psychological symptoms and the item on overall Quality of life were not included in the analyses due to content overlap with depression and overall Quality of life. Each symptom in the ESAS is scored on a scale from 0 (e.g. no lack of appetite) to 10 (e.g. worst possible lack of appetite).[27] Pain was measured by one question from the Brief Pain Inventory (BPI)[28] "pain at its worst during the last 24 hours". The item is rated on an 11-point numerical scale where 0 is "*no pain at all"* and 10 is "*worst possible pain*".

Depressive symptom severity: Depressive symptoms were assessed using the PHQ-9, a self-report questionnaire commonly used in medically ill samples, including cancer patients.[11 29] 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.[30,31] We have previously shown in this sample that the sum-score is likely conflated by high scores on somatic symptoms of depression that commonly overlap with symptoms of advanced cancer disease.[11] 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) and to receive oncological treatments (p<0.001), but less likely to receive opioids (p<0.001), than those not included (p<0.020). Moreover, the included patients had significantly higher physical functioning scores (KPS, p<0.001), 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 haemoglobin levels between the included and not-included.

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), increased symptom burden (more nausea and pain, appetite loss and shortness of breath and increased depression severity.)

Multivariate hierarchical model. In the final multivariate model, higher mGPS, low KPS, loss of appetite and more shortness of breath, 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 Block 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 sum-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), shortness of breath 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 substantial contribution of depression severity to QoL scores. The model explained 29% of the variance in QoL. Most of this was explained by depression (20%) while the other significant explanatory variables explained the remaining 9%.

Depression is prevalent[10] among advanced cancer patients and compromises QoL[8]. Although highly treatable[32], it is well documented that both doctors and nurses fail to detect emotional distress and patients themselves rarely disclose unless asked.[15] Further, anti-depressive medication is often started too late to have a benefit.[33] Given that the main aim of palliative care is to ensure the best possible QoL[34], our results emphasize the clinical importance of detecting and treating depressive symptoms early in the disease trajectory.

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 diseased populations.[5,6] Sociodemographic

variables that predict QoL in the general population[35] were not associated with QoL scores in our sample (i.e. age, gender, marital status and education). 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.[5,36] 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.[5]

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).[10] The mean QoL score of 50.5 is comparable to that reported in similar patient groups.[24] The corresponding numbers for the general population are 5-6% and 75, for depression[37] and QoL,[38] respectively.

Study strengths and limitations

The study has some limitations, notably its cross-sectional design which prevents us from making claims of causality between the variables. Further, as our model focuses on disease and treatment, psychosocial variables were not included, such as social support, which are likely to contribute to QoL. 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 diseased 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.[11] 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 the ASCO[39]. Lastly, the data was collected during 2008-2009. As such current treatments may produce slightly different symptom profiles than that described in our sample.

Strengths of this study are firstly 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.[40] Hence, these results add to the literature by suggesting that not only subjective symptoms, but also objective indicators of disease burden contribute to impaired QoL.

In this large, well characterized sample of patients with advanced cancer, we found that the severity of depression had by far the strongest impact on patients' QoL, irrespective of disease factors, prognostic factors and symptom burden. As such, our findings serve as reminder of the essential role that attention 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: Shortness of breath	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:					
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[7]	141	25.0%	85	17.5%	
None	157	27.9%	227	46.8%	
Opioids	291	33.5%	314	40.3%	<0.001
mGPS[8]					
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] Other oncological treatments include: radiotherapy without or with chemotherapy, hormone therapy and/or other anti-tumour treatments

[8]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.

	Univariate	**Mulitvariate**				
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
Medical							
2 **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**
	Shortness of breath	-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 shortness of breath 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)

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