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Independent contributors to overall quality of life in people with advanced cancer

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Background: The definition of health for people with cancer is not focused solely on the physiology of illness and the length of life remaining, but is also concerned with improving the well-being and the quality of the life (QOL) remaining to be lived. This study aimed to identify the constructs most associated with QOL in people with advanced cancer.

Methods: Two hundred three persons with recent diagnoses of different advanced cancers were evaluated with 65 variables representing individual and environmental factors, biological factors, symptoms, function, general health perceptions and overall QOL at diagnosis. Three independent stepwise multiple linear regressions identified the most important contributors to overall QOL. R^2 ranking and effect sizes were estimated and averaged by construct.

Results: The most important contributor of overall QOL for people recently diagnosed with advanced cancer was social support. It was followed by general health perceptions, energy, social function, psychological function and physical function.

Conclusions: We used effect sizes to summarise multiple multivariate linear regressions for a more manageable and clinically interpretable picture. The findings emphasise the importance of incorporating the assessment and treatment of relevant symptoms, functions and social support in people recently diagnosed with advanced cancer as part of their clinical care.

Cancer will develop in 45% of men and 40% of women during their lifetime, and about 1 in 4 will die of the disease (Marrett *et al*, 2008). The survival rates for most tumours are, however, continually improving owing to earlier detection, continued improvement in treatment therapies and better general medical management (Marrett *et al*, 2008). Owing to its improved survival, cancer is now considered a chronic disease (Canadian Academy of Health Sciences, 2010), and as a result, concerns about the well-being and the quality of life (QOL) of people with cancer has become paramount in clinical research (Food and Drug Administration, 2006). Health-care professionals are also becoming increasingly exposed to the benefits of assessing QOL in daily clinical practice. But the understanding of the scientific basis underlying QOL assessment still needs to be established (Osoba, 2007).

A comprehensive model of health-related QOL (HRQL) was developed by Wilson and Cleary (1995). This conceptual model suggests causal links among biological and physiological factors, symptoms, functional levels, general health perceptions and overall QOL. Individual and environmental characteristics also influence each of the components of the model (Wilson and Cleary, 1995). The Wilson and Cleary Model of HRQL for people with cancer can be seen in Figure 1.

The Wilson and Cleary model was partly assessed for patients with gastrointestinal bleeding (Sousa and Williamson, 2003), Parkinson's disease (Straits-Troster *et al*, 2000; Chrischilles *et al*, 2002), heart disease (Bennett *et al*, 2001; Heo *et al*, 2005; Lee *et al*, 2005a; Mathisen *et al*, 2007), HIV/AIDS (Wilson and Cleary, 1996, 1997; Sousa *et al*, 1999; Cosby *et al*, 2000; Hays *et al*, 2000; Sousa and Chen, 2002; Cunningham *et al*, 2005; Sousa and Kwok, 2006),

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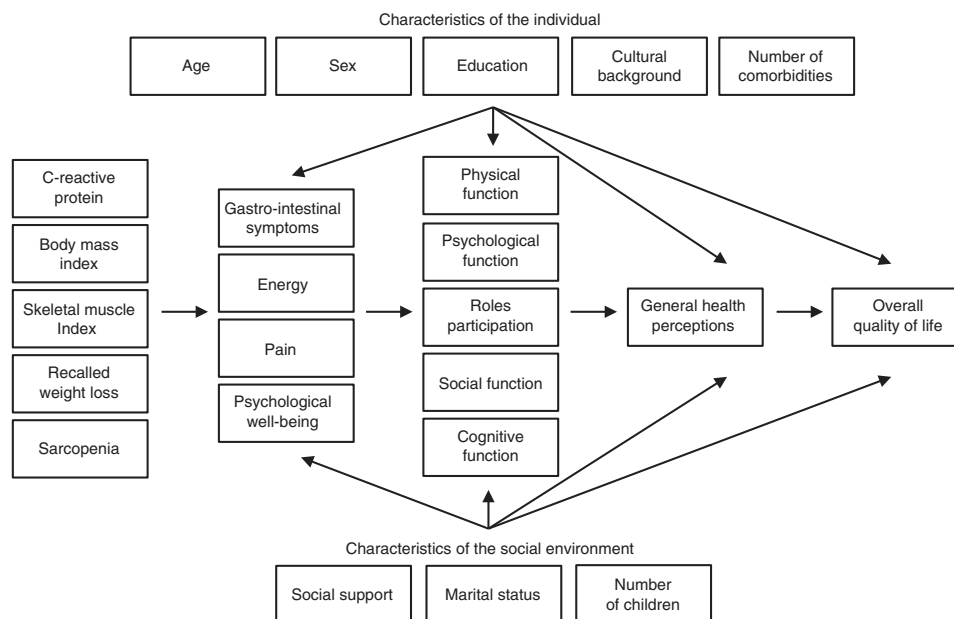


Figure 1. The Wilson and Cleary model of health-related quality of life in people with advanced cancer.

renal disease (Molzahn *et al*, 1996). It was minimally examined in people with cancer, as only one study examined the model with survivors with Hodgkin's lymphoma (Wettergren *et al*, 2004).

The purpose of this study was therefore to estimate, for people with a newly diagnosed advanced cancer, the extent to which biological and physiological factors, symptoms, function and general health perceptions predict overall QOL, as hypothesised by the Wilson and Cleary Model of HRQL.

MATERIAL AND METHODS

Participants. Adults were recruited if they have had a recent diagnosis of advanced cancer and had been referred to the McGill University Health Center or the Jewish General Hospital oncology clinics, in Montreal, Canada. Advanced cancer was defined as unresectable stage 3A, 3B or 4 non-small-cell lung cancer; stage 3 or 4 upper gastrointestinal cancer; stage 4 colorectal, hepatobiliary or head and neck cancers; breast and prostate cancers with visceral metastases; and all stages of pancreatic cancers. The inclusion criterion included an estimated life expectancy of 3 months or more and an Eastern Cooperative Oncology Group Performance Status Score of 0 to 3 to represent varying degrees of disabilities but sufficient function to complete the assessments (Oken *et al*, 1982). Patients were not eligible if they were unable to comply with study instructions or if they had symptomatic brain metastases.

Procedure. The study was approved by the hospitals' Institutional Review Board. The eligibility of patients was verified by a member of their primary oncology team who also obtained verbal consent to be approached by study personnel. If patients consented to participate, an appointment was made for the assessment. At their first assessment, participants were assessed using patient-reported outcomes and direct measures representing the domains of the Wilson and Cleary conceptual model of HRQL. If patients refused to participate, sociodemographic information such as their age, their primary tumour origin and their gender were collected, as were their self-perceived health from 0 to 10. This was done to estimate whether there was a sampling bias between participants and non-participants.

Measurement. The measurement strategy included characterising the sample and selecting relevant items and domains from widely used health outcomes measures in cancer.

The outcome of interest in this study was the construct of overall QOL. One subscale and two single items were used to represent overall QOL: the existential domain of the McGill Quality Of Life Questionnaire (MQOL-existential), the single-item scale of the McGill Quality of Life Questionnaire (MQOL-SIS) and the QOL item of the Edmonton Symptom Assessment System (first version) (ESAS-QOL).

Fifty-seven explanatory variables and eight potential confounder variables were included in the analyses. The variables were chosen to represent the different domains of the Wilson and Cleary model. The measures used and their psychometric properties are fully described in the Appendices A and B (Table A1 and A2), recognising that the individual items and subscales were the elements used in the analyses.

Biological and physiological indicators were also collected. These included C-reactive protein serum concentration levels, recent recalled weight loss at the time of diagnosis, the body mass index, the skeletal muscle index and the presence of sarcopenia.

In addition, personal factors such as age, sex, the site of the original tumour, the number of comorbidities, the highest level of education completed and the country of birth were recorded on the day of testing. Social environmental characteristics were also collected, such as the marital status and the number of children.

Statistical methods. Three different subscale/items (MQOL-existential, MQOL-SIS and ESAS-QOL) represented the outcome construct, overall QOL. Consequently, three independent analyses were performed to determine the most important contributors of overall QOL.

Descriptive statistics were used to characterise the participants and the distribution of variables. Mean values and standard deviations for continuous variables, as well as frequencies and percentages for categorical variables, summarised patients' characteristics. Age, sex, primary tumour site, years of education, cultural origin, number of comorbidities, number of children and marital status were examined for their potential for confounding.

Univariate linear regressions were used to screen the associations between the 57 potential contributors to each representation

of overall QOL. Variables that were associated with one of the QOL measures at *P*-value below or equal the 0.1 level were retained for the further analyses.

Bivariate correlations between the retained variables and the outcomes were examined using Pearson, polychoric and polyserial correlation coefficients. All assumptions of linear regression were examined, and there were no serious violations.

Three independent forward stepwise multiple linear regressions were performed to predict overall QOL. The 10 variables explaining the most variability per outcome were ranked by partial *R*² order. Effect sizes were also estimated for these variables using *t*-values (Cohen, 1988; Liang *et al*, 1990), which is a quantitative similar to Cohen's *d*. In the context of linear regression, the *t*-value corresponds to the difference in least-squares estimators divided by the standard error of the least-squares estimators. In an attempt to identify constructs with more consistent associations with overall QOL, the partial *R*² rankings and effect sizes of the identified contributing variables were averaged per construct and across all three outcomes of overall QOL.

Stepwise multiple linear regression is an analytical approach that has the capacity to select a statistical model 'when there is a large number of potential explanatory variables and no underlying theory on which to base the model selection' (Pace, 2008). This automatism of the procedure has been previously described as its limitation. However, in this study, the Wilson and Cleary theoretical model of HQOL directed the selection of the variables included in the analyses. Also, this statistical approach has the advantage of preventing bias imposed by the investigators upon the selection of final model.

All statistical analyses were carried out using the Statistical Analysis Systems version 9.2.

RESULTS

Description of the sample. Three thousand seven hundred fifty one patients were screened for eligibility. Of the 388 eligible patients, 203 patients (52.3%) consented to participate and completed the initial evaluation (Figure 2).

The average age was 63 years (± 13) and 59.3% of participants were men. The most common primary tumour origins were the pancreas (22.6%), followed by lung (16.7%), and the colorectal tract (12.3%). Patient characteristics are presented in Table 1.

Sociodemographic information was collected from 157 patients who refused to participate. The age and gender distribution was similar in both the participants and the non-participants: the average age was of 67 years (± 11.6) and 56.1% were men. The most common primary tumours sites in these patients were the lung (18.5%), followed by the pancreas (14.7%) and head or neck (14.0%). Participants and non-participants were similar (*P*-value = 0.80) on perceived health rated on a scale of 0 to 10: 6.8 (± 2.1) and 6.0 (± 2.1), respectively.

The distributions of the three outcomes of overall QOL are presented in Figure 3. MQOL-Existential, MQOL-SIS and ESAS-QOL (rescored) all ranged from 0–10, 10 indicating best quality of life and 0 the worst. Participants rated their QOL similarly with all measures of overall QOL. The medians were 7.9 for MQOL-Existential and 7.0 for MQOL-SIS and ESAS-QOL. The inter-quartile ranges spanned 2 units for MQOL-Existential, 3 for MQOL-SIS and 4 for ESAS-QOL. Of the three outcomes of overall QOL, MQOL-Existential had a smaller distribution, not unexpected with a multi-item index.

Univariate associations. The screening of the associations between the 57 potential explanatory variables and each measure of overall QOL by simple linear regression led to the elimination of between 7 and 17 variables per outcome variable. Of the retained

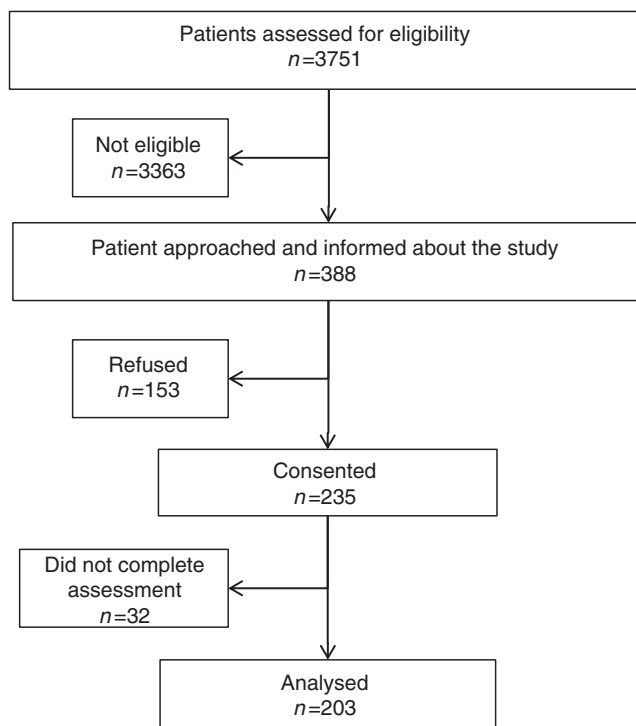


Figure 2. Flowchart.

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Participants (n = 203), (%)
Age (years) categories (mean: 63.3, s.d. 12.9)	
<35	7 (3.3)
36–50	23 (11.3)
51–64	72 (35.3)
≥65	101 (49.8)
Sex	
♂/♀	120/83
%	59.9/40.9
Primary tumour site	
Pancreatic	46 (22.6)
Lung	34 (16.7)
Colorectal	25 (12.3)
Upper GI	23 (11.3)
ENT	23 (11.3)
Breast	20 (9.8)
Hepatobiliary	17 (8.3)
Prostate	7 (3.4)
Urological	3 (1.5)
Unconfirmed primary origin	2 (1.0)
Ovarian	1 (0.5)
Retroperitoneal	1 (0.5)
Skin—basal cell	1 (0.5)
Number of comorbidities (mean 2.4, s.d. 1.5)	
0 (Cancer only)	74 (36.5)
1	51 (25.1)
≥2	78 (38.4)
Abbreviations: GI = gastrointestinal; s.d. = standard deviation	

variables, 34 had statistically significant associations with all three outcomes of overall QOL, 7 with two outcomes and only 3 were associated with only one outcome of overall QOL.

The univariate correlation coefficients were consistent with expectations. The correlation coefficients between the contributor variables and the outcomes varied from 0.01 to 0.59.

Stepwise multiple linear regression analyses. Table 2 summarises the rankings in partial R^2 , from 1 (the most important) to 10 (the least important), of the first 10 variables identified by the three independent stepwise regressions, using the ranking for

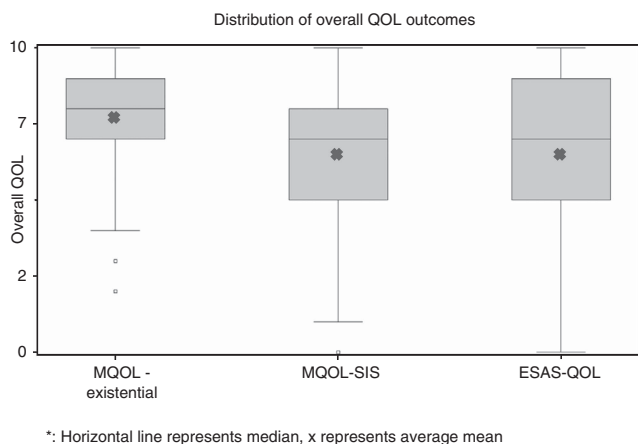
MQOL-Existential for the ordering of variables. Also presented are the effect sizes as measured by the t -test value.

When overall QOL was represented by MQOL-Existential, the variable with the highest partial R^2 was general health perception (GHP) from the RAND-36, followed by the psychological domain of the MQOL (rank 2) and social support domain (rank 3). When overall QOL was represented by MQOL-SIS, GHP (from MQOL) retained the first rank, followed by the psychological domain of the MQOL (rank 2), and an item of the Faact measuring appetite (rank 3).

When overall QOL was represented by ESAS-QOL, a subscale measuring physical function in the MFI held the first rank; an item measuring fatigue from the ESAS was ranked second, followed by the social support domain of the MQOL (rank 3).

The last two columns of Table 2 present the averages of the R^2 rankings and of the effect sizes. Using R^2 , the most important constructs contributing to overall QOL was social support and GHP (both with an average R^2 ranking of 3.0), followed by psychological distress, and relatively closely by fatigue. Using effect sizes, the same general order of the most important contributors remained. However, the effect sizes identified social function as much an important contributor. Both R^2 and effect sizes ranked physical function and symptoms profile in the same order. The two methods of average ranking produced statistically similar hierarchies when compared using the Wilcoxon signed-rank test ($P = 0.58$).

We represented the hierarchy of contributors of the overall QOL in people with advanced cancer as a pyramid analogous to Maslow's Hierarchy of Needs (Maslow, 1948) (Figure 4). As the pyramid identified needs, some constructs were modified to convey a positive meaning ('fatigue' was for instance modified to 'energy').



*: Horizontal line represents median, x represents average mean

Figure 3. Distribution of overall QOL outcomes.

Table 2. Relative ranking and effect sizes of items measuring symptoms, function and general health perception for QOL using adjusted R^2 -stepwise regression

	QOL outcomes							
	MQOL-existential (total $R^2 = 0.66$)		MQOL-SIS (total $R^2 = 0.69$)		ESAS-QOL (total $R^2 = 0.68$)		Average R^2 ranks ^a	Average effect sizes ^a (t-value)
	Partial R^2 rank	Effect size (t-value)	Partial R^2 rank	Effect size (t-value)	Partial R^2 rank	Effect size (t-value)		
Contributor constructs								
General health perception	1 ($R^2 = 0.32$)	4.9	1, 9 ^b ($R^2 = 0.50$)	8.6, 3.5 ^b			3.0	5.5
Psychological distress	2	6.5	2	3.3	7	2.3	3.7	4.0
Social support	3	7.1			3	4.0	3.0	5.6
Gastrointestinal symptoms							6.7	3.0
Smell	4	4.8						
Lack of appetite	5	2.8	3, 7, 10 ^b	3.9, 2.9, 2.0 ^b	10	2.5		
Taste	9	3.6			6	2.1		
Vomiting					4	2.6		
Stomach pain					8	2.0		
Interest in food					9	2.2		
Fatigue	6, 7 ^b	3.8, 4.3 ^b	4	3.2	2	5.2	4.2	4.2
Social function	8	4.0					8.0	4.0
Pain			6	2.3	5	2.2	5.5	2.3
Physical function	10	4.2	5, 8 ^b	3.5, 4.2 ^b	1 ($R^2 = 0.39$)	3.1	5.8	3.7

^aAverage R^2 rank: lower is first; Average effect sizes: higher is first.
^bBy individual item contribution. Also represented is the Partial R^2 of the 1st ranked item.

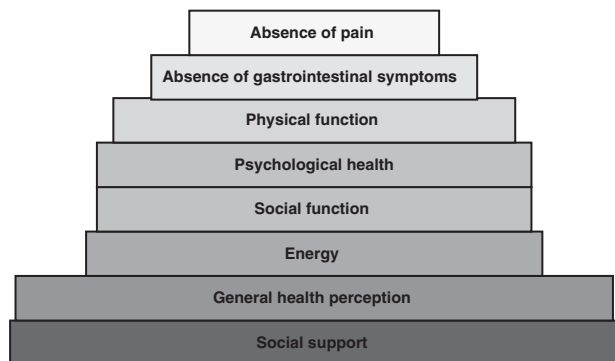


Figure 4. The hierarchy of contributors to QOL in people with advanced cancer.

DISCUSSION

Using multiple stepwise linear regression models, a large number of potential contributors to overall QOL were reduced to a manageable and interpretable clinical picture. Similar and sometimes different contributors were identified according to how the latent construct of overall QOL was represented.

Apart from random error, differences in the importance rankings by outcome undoubtedly arise from differences in the QOL outcomes themselves. Two outcomes were single items (MQOL-SIS and ESAS-QOL) and one was a subscale with a total score derived from averaging scores on 6 items (MQOL-Existential).

In the MQOL-SIS, the patient is asked to contemplate all aspects of his or her life (physical, emotional, social, spiritual and financial) (Cohen *et al*, 1997) and provide a value between 0 and 10. MQOL-Existential includes concerns regarding death, freedom, isolation and the meaning of life, as existential concerns have been demonstrated to be of great importance to people with a life-threatening illness and is under-represented in many measures assessing QOL (O'Connor *et al*, 1990; Fryback, 1993).

In contrast, ESAS-QOL is 1 of 10 visual analogue scales (VAS) describing how a person would best describe their health in the last 24 h. The health states include QOL and a variety of physical symptoms, usually of negative connotation such as fatigue, nausea, depression or pain (Bruera *et al*, 1991). It is therefore possible that although patients are asked to rate their general QOL, the context in which the item is asked is likely to influence the rating. Our study found that the contributing variables to the ESAS-QOL single-item were almost inversely ordered in terms of importance with respect to MQOL-Existential and MQOL-SIS.

We translated the findings from combining the results from the different the regression analyses into a 'pyramid of needs' mimicking Maslow's Hierarchy of Needs (Maslow, 1948) to emphasise that these are key areas of everyday life and function that people with threatened health need in order to continue to view life as worth living (World Health Organisation, 2001).

Social support was found to be the most important contributor to overall QOL meaning that, on average, people with advanced cancer who that reported being supported by their social surrounding also reported higher levels of overall QOL. By the term 'social support', we refer mainly to the resources provided by other persons (Cohen and Syme, 1985). It has also been defined as the cognitive appraisal of being 'reliably connected to significant others in a given social environment (Mathisen *et al*, 2007). Interestingly, it also fits with another identified contributor to overall QOL, social function. Social function can be defined as the actions and tasks required for basic and complex interactions with people in a contextually and socially appropriate manner (Cao *et al*, 2012). Therefore, the two concepts are closely related, as a socially functional individual will

likely have a strong social support system in place that could be used as a coping mechanism and vice-versa.

Social support is becoming recognised as an important contributor of overall QOL in people with cancer. In a study on the prevalence and contributors to the unmet needs and their association with QOL, 296 men with advanced cancer were evaluated. Social support scores significantly predicted total overall QOL scores, to the same extent that psychological or physical symptoms did (Hwang *et al*, 2004). Recently, several studies have been recommending measuring social support as part of the assessment of people with cancer as they are key elements of their well-being (Gallagher and Vella-Brodrick, 2008; Hahn *et al*, 2010; McCabe and Cronin, 2011). The role of social support at end-of-life is recognised and is one of the key roles played by volunteers in hospice system (Pesut *et al*, 2012).

Other important contributors to overall QOL were fatigue, psychological distress, pain and physical function. This is consistent with the published literature. Pain, depression and fatigue are highly prevalent in cancer patients, and they often coexist. Laird *et al* (2011) recently identified that pain, depression and fatigue was an identifiable symptom cluster in a cohort of advanced cancer patients and is associated with reduced physical functioning. Similarly, a study on 1630 stage 3 and 4 Danish cancer patients identified the most prevalent symptoms contributing to a deterioration of QOL (Johnsen *et al*, 2009) as being fatigue (57%; severe 22%) followed by reduced role function, insomnia and pain (Johnsen *et al*, 2009). The importance of the prevalence of these symptoms is such that in 2003, the National Institute of Health convened a State-of-the-Science Conference on pain, depression and fatigue symptom management in people with cancer in order to identify directions for future research (Patrick *et al*, 2003).

The self-reported overall QOL found in our study was strikingly similar to other studies with comparable populations. Lowe *et al* (2009) evaluated 50 adult advanced cancer patients with estimated life expectancies of 3 to 12 months from outpatient palliative care clinic and home care. Patients obtained a mean QOL score of 7.4 ± 1.4 on the MQOL-Existential and 6.1 ± 2.0 on ESAS-QOL (scale reversed from the original score of 3.9 ± 2.0) (Lowe *et al*, 2009). Similarly, 38 patients with advanced cancer were evaluated using MQOL-Existential and obtained a mean score of 7.9 ± 1.2 (Sherman *et al*, 2006). The same can be observed for reports of the MQOL-SIS: Jones *et al* (2010) obtained a mean MQOL-SIS score of 6.1 ± 1.4 when assessing 211 cancer patients admitted to an acute palliative care unit in a comprehensive cancer center.

This study included only patients with advanced disease, so the results may not be generalise to patients at the early stages of the disease. Regression approaches identify only those variables that, in the presence of all others, make a unique and direct contribution to the outcome, here overall QOL. A limitation is that variables which impact indirectly through other variables are not identified; nevertheless this approach provides a minimum portfolio of variables, which would be a starting in developing a more complex model requiring structural equation modelling (SEM). Another limitation of this approach is that the latent construct of overall QOL had to be modelled as different variables; SEM would allow the different representations of overall QOL to contribute statistically to a latent variable.

We demonstrated a novel way of using multivariate linear regressions to make sense of a large amount of information to a more manageable and clinically interpretable picture. However, the variation in the contributors to QOL has relevant implications for the clinical management of patients with advanced cancer. Depending on the instrument used, the focus of the interventions by the various health professionals would be different. Also, in the research setting, the choice of the instrument will greatly influence the 'measured' change in QOL secondary to the intervention(s) under study.

Social support is identified as the most important contributor to overall QOL in people with a recent diagnosis of advanced cancer. For health-care practitioners, this translates into assessing or asking patients recently diagnosed with cancer about their social networks and support and to arrange access for support when it is absent. The results also suggest paying particular attention to assessing and controlling physical function, fatigue, psychological distress, pain and gastrointestinal symptoms from the time of diagnosis. This would indicate that a team approach to measurement and care through the involvement of health-care professionals whose expertise lie in these domains (physical and occupational therapists, psychologists, social workers, nutritionists and palliative care physicians) would complement usual oncology care.

An interdisciplinary team approach, with a particular focus on physical function and fatigue, was found to be associated with improvement in overall QOL for patients with head and neck cancer (Eades *et al*, 2013). A recent clinical trial on the effect of early involvement of palliative care physicians and nurses in the care of patients with advanced lung cancer reported a significant improvement in overall QOL for the intervention group compared with patients receiving usual care (Temel *et al*, 2010). As the outcome for this study included items measuring physical function and fatigue, the effect may have been larger if the team had included health-care professionals with specialized expertise in those domains.

The involvement of health-care professionals with specific expertise in the management of cancer-related symptoms, psychological distress and loss of physical and social functions, supported by the integrated involvement of volunteers (Pesut *et al*, 2012), should be considered the new standard of care for patients with advanced cancer with decreased overall QOL. This is particularly important as fewer than 10% of oncology patients have been reported to receive psychosocial therapy (Lee *et al*, 2005b).

Modern health-care emphasises patient-centered care defined by a focus on outcomes that people notice and care about including, not only survival, but also function, symptoms and modifiable aspects of QOL (Patient-Centered Outcomes Research Institute, 2013). Thus, the measurement and optimisation of the contributors to QOL, such as those identified in this study, would be necessary components of a patient-centered oncology program.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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APPENDIX A

Table A1. Description and Psychometric Properties of the Measures

Measure	Description of measure	Psychometric properties
McGill QOL Questionnaire (MQOL)	The McGill Quality of Life Questionnaire (MQOL) was designed to measure QOL at all stages of a life-threatening illness, from diagnosis to cure or death (Cohen <i>et al</i> , 1995, 1996b, 1997, 2001; Cohen and Mount, 2000). It comprises 16 self-report items that are rated on a scale of 0 (the worst) to 10 (the best) and based on a two-day time frame. Five domains (physical symptoms, psychological symptoms, existential well-being, physical well-being and support) are computed from the score or the mean scores of 1 to 6 items. In addition, the MQOL	Good levels of reliability and validity in people with cancer (Cohen <i>et al</i> , 1995; 1996b, 1997, 2001; Cohen and Mount, 2000). Construct validity and internal consistency reliability of the domains was demonstrated in other palliative populations as well (Cohen <i>et al</i> , 1996a, 1997).

Table A1. (Continued)

Measure	Description of measure	Psychometric properties
	includes a single-item scale (MQOL-SIS), also scored from 0 to 10, and constructed to measure overall QOL.	
Edmonton symptom assessment system (ESAS)	The ESAS is a 10-item symptom visual analogue scale (VAS) developed for use in symptom assessment of palliative care patients (Richardson and Jones, 2009). The patients rate the severity of the following nine symptoms: pain, fatigue, nausea, depression, anxiety, drowsiness, lack of appetite, itching and shortness of breath on a 10-cm line. The severity for each symptom is rated from 0 to 10, 0 being an absent symptom and 10 being of the worst possible severity. There is an additional	An acceptable level of validity and reliability of the measure has been reported (Chang <i>et al</i> , 2000; Nekolai-chuk <i>et al</i> , 2008; Richardson and Jones, 2009).

Table A1. (Continued)

Measure	Description of measure	Psychometric properties
	VAS assessing quality of life.	
Preference-based cancer index (PBCI)	The Preference-based cancer index is an adaptation from the preference-based stroke index, a collection of items intended to supplement the EQ-5D index (Poissant <i>et al</i> , 2003). It includes 10 items with a three-point Likert-type response scale assessing walking, climbing stairs, physical activities/sports, recreational activities, work, driving, speech, memory, coping and self-esteem. A cumulative score can be obtained from these preference weights (Poissant <i>et al</i> , 2003).	Content validity and construct validity of the measure has been demonstrated (Poissant <i>et al</i> , 2003).
Functional assessment of anorexia/cachexia therapy (FAACT)	The FAACT consists of 27 Likert-type items of the symptoms associated with cancer and its treatments, scored from 0 to 4 anchored with 'not at all' to 'very much', with total quality of life score ranging from 0 to 108. The FAACT includes the FACT-G, with an additional 12 items of 'additional concerns' that refer to problems related to cachexia or anorexia (Ribaudo <i>et al</i> , 2000). In our assessment, we only included the 12 items relating to the cachexia/anorexia symptoms.	Reliability and validity of the FACT and the FAACT measurement system have been recognised (Ribaudo <i>et al</i> , 2000).
RAND short form 36-item health survey (RAND-36)—version 1	The RAND-36 is a generic health-related quality of life measure that assesses 8 health concepts: physical and social function, usual roles activities, pain, vitality, mental health, and perception of health in general. Each item is scored on a dichotomous, three or five-point categorical scale; subscale scores range from 0 to 100. Physical and mental summary scores can also be constructed (Hays <i>et al</i> , 1993).	Reliability, validity and responsiveness have been largely demonstrated in patients with a variety of acute and chronic conditions (Hays <i>et al</i> , 1993; Wood-Dauphinee <i>et al</i> , 1998).
EuroQol-5D (EQ-5D)	The EQ-5D comprises two sections, the EQ-5Dindex and the EQ-5DVAS. The EQ-5Dindex is a 5-item standardized generic measure	It has been widely used in studies of people with cancer (Norum, 1996) and it yields comparable results to other well-known

Table A1. (Continued)

Measure	Description of measure	Psychometric properties
	of HRQL measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression with a three-point response scale. The EQ-5DVAS is a 0–100 thermometer scale that assesses self-perceived health status.	measures (de Haan <i>et al</i> , 1993; Goodyear and Fraumeni, 1996; Norum, 1996).
Taste and smell indicators (TSI)	The taste and smell indicators (TSI) consist of two single-item indicators asking for disturbances in smell and in taste, with a three-point Likert-type response scales associated with the anchors 'no disturbances', 'moderate disturbances' and 'severe disturbances or cannot smell/taste at all'.	It yields comparable results to other well-known measures (de Haan <i>et al</i> , 1993; Goodyear and Fraumeni, 1996; Norum, 1996).
Word and digit recall questions (WDR)	To assess visual memory, we derived the word recall question from the delayed word recall test, a test originally developed to facilitate the early diagnosis of Alzheimer's disease (O'Carroll <i>et al</i> , 1997). The digit sequence learning test is a test of attention, short-term memory, and associative learning (Benton <i>et al</i> , 1983). Subjects are asked to repeat a string of digits immediately after hearing them, first in direct and then in reverse order. The total number of correctly repeated digit string sequences was tallied.	
Multidimensional fatigue inventory (MFI)	The Multidimensional fatigue inventory (MFI) is a 20-item self-report measure of fatigue with five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity, and 4 items per dimension, each scored from 1 to 5. The total score ranges from 4 to 20, a higher score indicating more fatigue.	The measure was evaluated with cancer patients receiving radiotherapy and was found to have good internal consistency, construct validity and convergent validity (Smets <i>et al</i> , 1995; Schneider, 1998; Meek <i>et al</i> , 2000; Fillion <i>et al</i> , 2003).
Modified 'community healthy activities model program for seniors physical activity measure' (modified CHAMPS)	The CHAMPS is a self-report measure of physical activity, comprising 40 activities evaluated according to the total number of hours of activity done in the past week. We used a modified version of the CHAMPS resulting in the physical	The measure has been shown to be reliable, valid and responsive in the elderly in the community (Stewart <i>et al</i> , 2001a, 2001b).

Table A1. (Continued)

Measure	Description of measure	Psychometric properties
	activities done in the past week in total hours. The numbers of hours and the type of category was then transformed into a respective mean metabolic equivalent (MET) intensity level (Ainsworth <i>et al</i> , 2000).	
Six minute walk test (6MWT)	The 6 min walk test (6MWT) is a submaximal functional test of walking endurance (Solway <i>et al</i> , 2001). The distance walked was recorded both at the first 2 min and for the full duration of the test at 6 min. The data included here are for the test at 2 min to maximise the data obtained, as some fragile patients could not complete the six minutes of the test.	The 6MWT has been evaluated in several different populations and is a valid and reliable measure (Solway <i>et al</i> , 2001).
Timed 'up and go' (TUG)	The timed up and go is a quick and practical test of basic mobility skills suitable for frail elderly persons. The score, is the time, in seconds, taken to stand up from a chair, walk 3 m back-and-forth, and sit down. Higher scores indicate greater impairment of mobility.	Concurrent validity (Podsiadlo and Richardson, 1991; Venturini <i>et al</i> , 1995) has been demonstrated with correlations with gait speed, walking speed $r=0.71-0.96$, the Berg balance scale, and the Barthel index ($r = -0.51$).
Walking speed	Gait speed is a physical characteristic derived from directly measuring the parameters of distance and time. It has been associated with strength of the affected lower extremity, cadence and stride length, balance, degree of lower extremity motor recovery, and functional mobility (Holden <i>et al</i> , 1986). Standardized instructions are to walk at a 'comfortable' or 'maximum' speed along a walkway typically ranging from 2 to 20 m (Fransen <i>et al</i> , 1997). In this study, we instructed patients to walk at a comfortable pace speed over a distance of 10 m, and the time taken to complete the middle 5 m distance was recorded.	Gait speed is considered a valid measure of walking ability as it correlates with functional mobility, degree of independence in walking, and many different gait parameters (Holden <i>et al</i> , 1986; Nakamura <i>et al</i> , 1988; Fransen <i>et al</i> , 1997).

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APPENDIX B

Table A2. Classification of Variables and Constructs Measured			
Outcome variables	Construct measured	Measurement scale	Units/properties
MQOL-SIS—stand alone item	Quality of life	Continuous	0–10 VAS scale, higher is better
MQOL-existential domain	Quality of life	Continuous	Mean score of 6 items, scale 0–10, higher is better
ESAS-QOL item	Quality of life	Continuous	0–10 VAS scale, lower is better
Exposure variables	Construct measured	Measurement scale	Original units/properties*
Biological variables			
Body mass index	Muscle wasting	Continuous	kg m ⁻²
Skeletal muscle index (skeletal muscle mass/total mass x 100%)	Muscle wasting	Continuous	%
Sarcopenia	Muscle wasting	Continuous	No; yes
C-reactive protein	Systemic inflammation	Continuous	mg l ⁻¹
Recalled weight loss	Recent weight loss	Categorical	None; 2–5%; > 5%
Symptoms			
Gastrointestinal symptoms			
Faact o2	Vomiting	Categorical—ordinal	0–4 scale, higher is worse
ESAS nausea	Nausea	Continuous	0–10 VAS scale, lower is better
ESAS appetite	Appetite	Continuous	0–10 VAS scale, lower is better
Faact c6	Appetite	Categorical—ordinal	0–4 scale, higher is better
Faact act6	Interest in food	Categorical—ordinal	0–4 scale, higher is worse
Faact act7	Difficulty eating rich food	Categorical—ordinal	0–4 scale, higher is worse

Table A2. Continued			
Exposure variables	Construct measured	Measurement scale	Original units/properties*
Faact act10	Getting easily	full categorical—ordinal	0–4 scale, higher is worse
Taste and smell			
Taste item	Taste	Categorical—ordinal	0–2 scale, higher is worse
Smell item	Smell	Categorical—ordinal	0–2 scale, higher is worse
Faact act 3	Taste	Categorical—ordinal	0–4 scale, higher is worse
Pain			
ESAS pain	General pain	Continuous	0–10 VAS scale, lower is better
EQ-5D pain	General pain	Categorical—ordinal	0–2 scale, higher is worse
Faact act 11	Stomach pain	Categorical—ordinal	0–4 scale, higher is worse
RAND-36—pain subscale	General pain	Continuous	0–100 scale, higher is better
Fatigue			
ESAS fatigue	Fatigue	Continuous	0–10 VAS scale, lower is better
MFI—general fatigue subscale	Fatigue	Continuous	4–20 subscale, higher is worse
RAND-36—vitality subscale	Energy	Continuous	0–100 scale, higher is better
Psychological symptoms			
MQOL—psychological domain	Nervousness, being afraid, depressed, sad	Continuous	Mean score of 4 items, 0–10, higher is better
ESAS depression	Depression	Continuous	0–10 VAS scale, lower is better
ESAS anxiety	Anxiety	Continuous	0–10 VAS scale, lower is better
EQ-5D depression/anxiety	Depression/anxiety	Categorical—ordinal	0–2 scale, higher is worse
RAND-36—mental health subscale (MHI)	Nervousness, being calm, depressed, 'blue', happy	Continuous	0–100 scale, higher is better

Table A2. Continued			
Exposure variables	Construct measured	Measurement scale	Original units/properties*
Cognition and concentration			
Word recall	Memory	Continuous	0–5, higher is better
Mental reversal	Concentration	Continuous	0–5, higher is better
Delayed recall	Memory	Continuous	0–5, higher is better
Digit series repeats forward	Memory/concentration	Continuous	0–16, higher is better
Digit series repeats backwards	Memory/concentration	Continuous	0–16, higher is better
PBCI memory	Memory	Categorical—ordinal	0–2 scale, higher is worse
MFI—mental fatigue	Concentration	Continuous	4–20 subscale, higher is worse
FUNCTION			
Physical function			
EQ-5D mobility	Mobility	Categorical—ordinal	0–2 scale, higher is worse
EQ-5D self-care	Self-care	Categorical—ordinal	0–2 scale, higher is worse
EQ-5D usual activities	Usual activities	Categorical—ordinal	0–2 scale, higher is worse
MFI—physical fatigue	Physical function	Continuous	4–20 subscale, higher is worse
RAND-36—physical function subscale	Physical function	Continuous	0–100 scale, higher is better
MFI—reduced activity	Physical activities	Continuous	4–20 subscale, higher is worse
PBCI—Function Subscale (mean score of 5 items)	Walking, stairs, participating in demanding activities, work, driving	Continuous	0–2 subscale, higher is worse
2 MWT distance	Functional walking capacity	Continuous	Metres
TUG	Basic mobility	Continuous	Seconds
Comfortable gait speed	Walking ability	Continuous	Metres/seconds
Average METS per week	Average weekly activity level	Continuous	METS
Psychological function			
PBCI coping	Coping	Categorical—ordinal	0–2 scale, higher is worse
PBCI self-esteem	Self-esteem	Categorical—ordinal	0–2 scale, higher is worse
MFI—reduced motivation subscale	Desire to engage in activities	Continuous	4–20 subscale, higher is worse
Social function			
RAND-36—social subscale	Social function	Continuous	0–100 scale, higher is better

Table A2. Continued			
Exposure variables	Construct measured	Measurement scale	Original units/properties*
Role function			
RAND-36—role emotional subscale	Role function	Continuous	0–100 scale, higher is better
RAND-36—role physical subscale	Role function	Continuous	0–100 scale, higher is better
General health perception			
EQ-5D VAS	GHP	Continuous	0–100 VAS, higher is better
RAND-36—GHP Subscale	GHP	Continuous	0–100 scale, higher is better
MQOL—physical well-being	Physical health perception	Continuous	0–10 VAS, higher is better
Potential confounding variables	Construct measured	Measurement scale	Units/properties
Individual characteristics			
Sex	Sex	Binary	0 = female 1 = male
Age	Age	Continuous	Years
Number of comorbidities	Comorbidities	Considered continuous	1–7, Higher number indicates more
Individual characteristics (continued)			
Cancer type	Primary tumour site	Categorical—ordinal	Eight main tumour sites
Educational level	Proxy to Socio-economical status	Categorical—ordinal	Eight levels corresponding to highest degree obtained
Nationality	Cultural influence	Categorical—nominal	Country of birth
Social support characteristics			
Marital status	Social support	Categorical—nominal	Six marital statuses
Number of children	Social support	Continuous	Number of children
Someone they can trust and confide in	Social support	Binary	No; yes
Someone who would be able to provide help as long as they would need it	Social support	Binary	No; yes
MQOL-support domain	Social support	Continuous	Mean score of two items, 0–10, higher is better
Abbreviations: ESAS = edmonton symptom assessment system (original version); EQ-5D = EuroQoL-5D; Faact = functional assessment of anorexia/cachexia therapy; MFI = multidimensional fatigue inventory; MQOL = McGill quality of life questionnaire; PBCI = preference-based cancer index; RAND-36 = RAND short form 36-item health survey (RAND-36)—version 1; VAS = visual analogue scales. Some of the items of the Faact and the MFI, as well as all items of the ESAS, the EQ-5D index, the PBCI, and the taste and smell items were rescored so that a higher score indicates better health status. Rescoring for some variables took place after the examination of the frequencies to account for categories with no or little observations.			