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original article

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Impact of fatigue on overall quality of life in lung and breast cancer patients selected for high-dose radiotherapy

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Background: Although studies show that cancer patients consider fatigue as an important problem, few, if any, studies have quantified the impact of fatigue on overall quality of life (QoL) in cancer patients. In the present study, we evaluated the relative impact of different QoL domains/subscales, including fatigue, on overall QoL in cancer patients preceding radiotherapy.

Patients and methods: Sixty-four patients with lung or breast cancer selected for high-dose radiotherapy on the primary tumour completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Multivariate models were fitted to define the impact of QLQ-C30 subscales, including fatigue, on overall QoL.

Results: Of all QLQ-C30 subscales, fatigue showed by far the strongest univariate correlation with overall QoL ($r = -0.76$, $P < 0.001$); correlations for functioning subscales ($r = 0.44$–0.55) and symptom subscales ($r = -0.31$ to -0.45) were considerably lower. In multivariate analyses, adjusting for potential confounders, fatigue was the only subscale that independently contributed to overall QoL (standardized regression coefficient -0.57, $P < 0.001$).

Conclusion: Our results indicate that, of all QoL domains/subscales, fatigue is by far the predominant contributor to patient-perceived overall QoL in both lung and breast cancer patients preceding high-dose radiotherapy.

Key words: breast cancer, EORTC QLQ-C30, fatigue, lung cancer, quality of life, radiotherapy

original article

introduction

Over the last decade, quality of life (QoL) measures have been routinely incorporated in oncological clinical trials; also, the use of QoL measures in clinical settings is strongly encouraged because their value in cancer patient management has now been established [1]. QoL is generally considered as a multidimensional construct, which includes several key dimensions [2].

Fatigue (defined as a general feeling of debilitating tiredness or loss of energy) is one of the most common QoL-related symptoms in cancer today [3–8]. The occurrence of fatigue varies across tumour sites [6, 9, 10] and treatment stage [6, 9, 11–14]. Lung cancer patients undergoing radiotherapy had the highest levels of fatigue relative to patients of other tumour types [6]. For patients and oncologists, improving the QoL of cancer patients requires a heightened awareness of fatigue, a better understanding of its impact and improved communication and familiarity with interventions that can reduce its debilitating effects [15]. However, despite previous surveys on patients' subjective and conscious valuation of the impact of fatigue on daily life, few, if any, studies so far have made an attempt to quantify the impact of fatigue, relatively to other QoL domains, on overall QoL in cancer patients before high-dose radiotherapy. In the present paper, we will address this issue using the multilevel QoL structure as proposed by Spilker [16]. According to these authors, the top level of QoL is referred to in clinical trial literature as 'global QoL assessment' and can be interpreted as an overall impression of 'an individual's overall satisfaction with life and one's general sense of personal well-being'. This level corresponds to the World Health Organization (WHO) definition of QoL as "a state of complete physical, mental and social well-being and not merely the absence of diseases and infirmity." The second or middle level represents several broad dimensions or domains of QoL such as physical/somatic, psychological and social functioning. Finally, the bottom level contains the components of each domain that are specifically assessed as items in QoL questionnaires. For example, functional limitations or activities of daily living are part of the physical domain of QoL; measures

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of anxiety or depression are specific aspects of the domain of psychological functioning, whereas participation in social activities can give an impression of the domain of social functioning.

Spilker's model [16] assumes that QoL variables at a lower level determine QoL variables at a higher level. This relation between lower and higher QoL levels has great practical relevance because it gives insight in the consequences of an illness for patients in terms of valuation of life. An overall judgement of QoL requires patients to evaluate several life domains, and to combine the weightings of these domains into a 'generic value judgement' of life.

So far, only few studies have compared disorders with respect to QoL [17–21]. Arnold et al. [17], for example, recently studied the contribution of physical, social and psychological functioning to patients' valuation of overall QoL in a cross-sectional study in healthy subjects and patients with chronic disorders. No cancer patients were, however, included in that study. Linear regression analyses showed that the domain of psychological functioning contributed to overall QoL for all disorders, whereas physical and social functioning contributed to overall QoL for some disorders only.

The contribution of different QoL dimensions to overall QoL in cancer patients could differ from chronic diseases for several reasons. First, in contrast with many chronic diseases, cancer is perceived as a more acutely or subacutely life-threatening disease and secondly, symptoms such as fatigue, anorexia and pain play a predominant and specific role in the QoL of cancer patients [22–24], and might therefore be valuated differently by cancer patients relative to patients with other acute and chronic diseases.

Therefore, the aim of the present study was to quantify the impact of fatigue, relative to other QoL domains/subscales, on overall QoL in cancer patients preceding radiotherapy.

patients and methods

study population and design

The present study used a cross-sectional design to assess fatigue, several QoL domains and overall QoL, in a population of lung and breast cancer patients selected for curative high-dose radiotherapy (≥50 Gy) on the primary tumour. Seventy patients older than 18 years of age and with WHO performance status (PS) zero to two were invited to participate [25]. Both breast cancer patients and nonsurgery lung cancer patients were included. Before radiotherapy, patients were asked to complete a measurement tool including a demographic profile and the well-known European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). After permission, both the patient and their radiation oncologist signed for informed consent. The study was approved by the ethics committee of MAASTRO clinic, Maastricht, The Netherlands.

measurement instruments

Background variables included age, gender, body mass index (BMI), WHO PS and prior treatment. The EORTC QLQ-C30 (version 3.0) is a 30-item cancer-specific core questionnaire that addresses various domains of QoL [26]. It contains five function subscales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), three symptom subscales (fatigue, pain and nausea/vomiting), two single items assessing global health and 'overall' QoL and a number of single items addressing various symptoms and perceived financial impact (for convenience, these are also called "subscales" throught this paper).

statistical analysis

Pearson's correlation analyses were calculated to study the relation between QoL subscales and overall QoL. As dependent variable 'overall QoL', we used item 30 of the EORTC QLQ-C30 ("How would you rate your overall quality of life during the past week?"). Linear regression models were fitted to investigate the impact of functioning and symptom subscales, including fatigue, on overall QoL. As independent variables, we included only 'substantial' QLQ-C30 subscales, defined as subscales and single items which individually explained at least 20% of the variance of overall QoL in the univariate analyses (i.e. subscales showing correlations with overall QoL of $r \geq 0.45$ or ≤ -0.45). In order to adjust for potential confounders, we first assessed univariate associations between overall QoL and age, gender, tumour type, tumour stage, pretreatment by chemotherapy (yes/no), BMI and WHO performance score. Since only tumour type, tumour stage, prior chemotherapy and WHO PS were significantly, albeit modestly, related with overall QoL (Pearson's correlations 0.26–0.28, $P < 0.05$), these variables were included as potential confounders in the regression models. To compare the impact of fatigue, relative to all other substantial subscales on overall QoL, two models were fitted: one model which included as covariates the substantial subscales of the somatic, psychological and social domains as covariates, but not fatigue and one model which included the same subscales as well as fatigue. An F-test (F change) was used to compare the variance (R^2) in overall QoL explained by different models.

Presented R^2 values in this paper are adjusted R^2 values throughout. Collinearity tests showed the absence of multicollinearity between any of the determinants included in the regression models. P values <0.05 (two tailed) were considered statistically significant.

results

patient characteristics

Six patients out of the 70 included patients refused to cooperate because of being too tired; the remaining 64 patients (91%) completed the EORTC QLQ-C30. Patient characteristics are presented in Table 1.

Mean age of the study population was 64 years, and the large majority of patients had WHO PS zero or one. Half of the lung cancer and a quarter of the breast cancer patients had been pretreated with chemotherapy. EORTC QLQ-C30 scores showed considerable impairment in QoL, especially in lung cancer patients, for the subscale 'global health status/QoL' and its components 'global health' (QLQ-C30 item 29) overall QoL (QLQ-C30 item 30), as well as for the subscales physical, role and emotional functioning, and for the symptom subscales fatigue, dyspnoea, pain, insomnia and appetite loss. Lung cancer patients were significantly more tired than breast cancer patients ($P < 0.01$); also, tumour stage, prior treatment with chemotherapy and lower WHO performance scores were associated with higher fatigue levels ($P < 0.05$).

contribution of different QoL subscales and domains to overall QoL

Univariate correlations between functional and symptom subscales of the QLQ-C30 and overall QoL are shown in Table 2.

Of all subscales, fatigue showed by far the strongest correlation with overall QoL ($r = -0.76$, $P < 0.001$). Other

Table 1. Characteristics of the study population ($N = 64$) by tumour type

	Lung cancer ($n = 29$)	Breast cancer ($n = 35$)
Age (years)	68.2 ± 10.8[a]	60.2 ± 12.4
Gender, female	45%	100%
Body mass index	22.8 ± 3.1	25.8 ± 3.9
WHO performance status		
0	20%	94%
1	50%	6%
2	10%	0%
Unknown	20%	0%
Prior treatment		
Chemotherapy	52%	26%
Surgery	0%	100%
Radiotherapy	0%	0%
Global health status/QoL[b]	53.7 ± 25.4	71.0 ± 23.6
Global health[c]	51.7 ± 24.9	69.0 ± 22.9
Overall QoL[d]	55.7 ± 29.6	72.9 ± 25.9
Functional subscales		
Physical functioning	56.1 ± 24.9	79.6 ± 20.8
Role functioning	46.6 ± 35.5	75.2 ± 30.3
Emotional functioning	62.6 ± 26.9	76.4 ± 19.3
Cognitive functioning	75.9 ± 20.7	87.1 ± 18.1
Social functioning	71.3 ± 29.5	82.9 ± 23.7
Symptom subscales/items		
Fatigue	51.7 ± 27.4	30.2 ± 29.8
Nausea and vomiting	15.5 ± 27.4	11.9 ± 24.1
Pain	33.3 ± 37.3	16.2 ± 26.1
Dyspnoea	44.8 ± 38.1	15.2 ± 31.7
Insomnia	32.1 ± 39.0	30.5 ± 33.7
Appetite loss	31.0 ± 39.8	15.2 ± 23.4
Constipation	23.0 ± 33.5	13.7 ± 26.1
Diarrhoea	3.4 ± 13.6	5.7 ± 18.9
Financial difficulties	8.3 ± 21.5	6.7 ± 15.8

[a]Values represent mean ± standard deviation on a scale from 0 to 100. Higher scores represent better levels for global health status, overall QoL and all functioning subscales; higher scores represent higher levels of symptoms/distress for all symptom subscales items (fatigue, pain, etc.).
[b]Global health status/QoL: QLQ-C30 subscale of combined items 29 and 30.
[c]QLQ-C30 item 29.
[d]QLQ-C30 item 30.
WHO, World Health Organization; QoL, quality of life.

subscales with statistically significant correlations with overall QoL were all functional subscales ($r = 0.44$–0.55) and (in order of decreasing magnitude) the symptom subscales loss of appetite, nausea/vomiting, insomnia, dyspnoea, pain and constipation ($r = -0.45$ to -0.31). The correlation between fatigue and overall QoL was independent of tumour type (lung cancer: $r = -0.74$; breast cancer: $r = -0.74$; both $P < 0.001$). Correlations between other subscales and overall QoL were also similar in lung and breast cancer patients (data not shown), except for dyspnoea [lung cancer: $r = -0.55$, $P < 0.01$; breast cancer: -0.10, not significant (NS)] and financial difficulties (lung cancer: $r = -0.20$, NS; breast cancer: -0.38, $P < 0.05$).

In Table 3, the independent contributions of QLQ-C30 subscales to overall QoL are shown. In these analyses, only

Table 2. Pearson's correlations between different EORTC QLQ-C30 subscales and overall QoL

	Correlation ($N = 64$)	P value
Physical functioning	0.550	<0.001
Role functioning	0.515	<0.001
Emotional functioning	0.515	<0.001
Cognitive functioning	0.441	<0.001
Social functioning	0.507	<0.001
Fatigue	−0.759	<0.001
Nausea and vomiting	−0.451	<0.001
Pain	−0.361	0.004
Dyspnoea	−0.416	0.001
Insomnia	−0.418	0.001
Appetite loss	−0.452	<0.001
Constipation	−0.314	0.012
Diarrhoea	−0.077	0.548
Financial difficulties	−0.280	0.026

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QoL, quality of life.

subscales explaining ≥20% of the variance of QoL in both tumour types combined (corresponding with univariate correlations ≥0.45 or ≤−0.45 in Table 2) are included. Two overall models are given: one showing the independent contributions of the combined subscales without fatigue and one model with the same subscales plus fatigue. It is seen that the overall model without fatigue explained 40% (adjusted R^2) of the variance of overall QoL, i.e. less than the fatigue subscale alone (53%). Comparison of these two models, i.e. without and with fatigue, showed that adding fatigue to the total model significantly increased the explained adjusted variance of overall QoL from 40% to 50% ($P < 0.001$). In contrast, the percentage of variance explained by fatigue alone (53%) was similar to or even higher than the explained adjusted variance by the total model including fatigue (50%); the difference was not statistically significant ($P = 0.69$). In the total model including fatigue, the fatigue subscale paid by far the highest individual contribution to overall QoL (standardized regression coefficient: -0.57, $P = 0.002$). In this model, none of the other subscales contributed significantly to overall QoL.

discussion

The aim of the present study was to investigate the impact of fatigue, relative to other QoL domains, on overall QoL in cancer patients preceding radiotherapy. Results showed that fatigue was by far the predominant determinant of overall QoL, showing a univariate correlation with overall QoL of −0.76. This correlation was independent of tumour type, and remained unchanged in multivariate analyses with adjustment for tumour type, tumour stage, pretreatment with chemotherapy and WHO performance score. In fact, fatigue alone explained a greater proportion of variance in overall QoL than the combined functional and symptom subscales of all other domains (somatic, psychological and social). This finding indicates that, in our study population, the impact of fatigue on overall QoL largely overruled the impact of any other functional and symptom subscales.

Table 3. Independent contributions of different EORTC QLQ-C30 subscales to overall QoL, adjusted for tumour type, tumour stage, prior chemotheraphy and WHO performance status ($N = 64$)

Subscale	**Model 1: total model without fatigue** ($R^2 = 0.400$***) estimate	**Model 2: total model including fatigue** ($R^2 = 0.502$***) estimate
Physical functioning	0.371*	0.178
Role functioning	−0.029	−0.132
Emotional functioning	0.307*	0.194
Social functioning	0.140	−0.016
Nausea and vomiting	−0.303*	−0.207
Appetite loss	−0.065	0.063
Fatigue	–	−0.574**

Estimates show standardized regression coefficients for different QoL subscales, on the basis of linear regression models with overall QoL as the dependent variable. Values of R^2 show the overall adjusted R^2 of the concerned regression model.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QoL, quality of life.

So far, little research has been conducted to quantitatively assess the empirical relations between physical, psychological and social domains and overall QoL in cancer patients. The contribution of specific domains to overall QoL may differ between diseases since different diseases may have a differential effect on the functioning of patients in different QoL domains. In a previous study in patients with different chronic disorders, but not cancer [17], the correlations between different functional QoL domains and overall QoL were considerably lower (mostly $r \leq 0.45$) than in our cancer population, and the variance in overall QoL explained by combined physical, psychological and social domains was <30% for all conditions except lung disorders (33%) and migraine (44%). Psychological functioning was the predominant determinant in all chronic conditions studied by Arnold et al. [17], whereas physical functioning contributed to overall QoL for lung disorders only. Fatigue was not evaluated as a separate QoL domain by these authors.

Fatigue is a symptom frequently encountered in cancer patients, due to either illness or treatment. Almost every patient suffers from fatigue during cancer treatment such as radiotherapy and/or chemotherapy, and in the scientific literature reported prevalence rates of fatigue are up to 99% [6, 14, 27, 28]. Research shows that chronic fatigue is associated with problems and limitations in different areas of life. Severe fatigue leads not only to physical restrictions but also to serious impairment in QoL, social activities and the ability to go to work [6, 14, 29, 30]. The present study, in which we evaluated the relation between fatigue scores of patients and their overall QoL scores on the EORTC QLQ-C30, corroborates the dramatic impact of fatigue on overall QoL in patients with cancer.

In our study, we purposely did not use the subscale global health status/QoL of the EORTC QLQ-C30 as the dependent variable because this subscale is the sum of two conceptually different items, which are related to global health (item 29) and overall QoL (item 30), respectively. Results, however, remained quite similar when we tentatively repeated all analyses using the global health status/QoL subscale (sum of items 29 and 30 of the QLQ-C30) as the dependent variable (data not shown), giving further support to the importance of fatigue in patients' valuation of global health and QoL.

Strengths of the present study are the relatively homogeneous study population with only two tumour types at a well-defined treatment stage, i.e. before high-dose radiotherapy, as well as the high level of participation of subjects. Our study population was originally selected to assess the validity of existing QoL questionnaires [31] as well as to explore patients' acceptability of these instruments [25]; therefore, we purposely included patients of two distinct tumour types with considerable anticipated variation in fatigue as well as physical and psychological distress. A high diversity of occurrence of fatigue across treatment sites has been reported, with higher fatigue levels in lung relative to breast cancer patients [6]. Despite these differences between patients with lung and breast cancer, the contribution of fatigue to overall QoL was remarkably similar in patients of these two tumour types, as shown by identical correlations between fatigue and overall QoL in both tumour types separately. Therefore, even though the relatively small number of subjects is a limitation of our study, it seems quite unlikely that a larger number of subjects would have changed its results. Although the present study was not aimed at investigating the aetiology of fatigue, tentative analyses indicated that the high level of fatigue in our patient population was unrelated to BMI, WHO score or haemoglobin levels (data not shown).

In conclusion, our results indicate that, in lung and breast cancer patients preceding radiotherapy, fatigue is by far the predominant contributor to patient-perceived overall QoL. Our results support the notion that fatigue in cancer patients is a major problem, which deserves yet more attention from health professionals, and that QoL in cancer patients might be improved markedly by interventions that effectively reduce fatigue.

Further research is needed to reproduce these results in patients of different tumour types and at different stages of disease and therapy, ranging from diagnosis to the palliative treatment stage.

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