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European Journal of Cancer 40 (2004) 1021–1030

European Journal of Cancer

www.ejconline.com

Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer

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Received 15 January 2004; accepted 21 January 2004

Presented at the Annual Meeting of the American Society of Clinical Oncology. Chicago, IL (USA). May 31–June 3, 2003.

Abstract

The potential value of baseline health-related quality-of-life (HRQOL) and clinical factors in predicting prognosis was examined using data from an international randomised phase III trial which compared doxorubicin and paclitaxel with doxorubicin and cylophosphamide as first line chemotherapy in 275 women with metastatic breast cancer. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the related breast module (QLQ-BR23) were used to assess baseline HRQOL data. The Cox proportional-hazards regression model was used for both univariate and multivariate analyses of survival. In the univariate analyses, performance status ($P<0.001$) and number of sites involved ($P=0.001$) were the most important clinical prognostic factors. The HRQOL variables at baseline most strongly associated with longer survival were better appetite, physical and role functioning, as well as less fatigue ($P<0.001$). The final multivariate model retained performance status ($P<0.001$) and appetite loss ($P=0.005$) as the variables best predicting survival. Substantial loss of appetite was the only independent HRQOL factor predicting poor survival and was strongly correlated ($|r|>0.5$) with fatigue, role and physical functioning. In addition to known clinical factors, appetite loss appears to be a significant prognostic factor for survival in women with metastatic breast cancer. However, the mechanism underlying this association remains to be precisely defined in future studies.

Keywords: Quality of life; Prognostic factor; Randomised controlled trial; Breast cancer

1. Introduction

Although there is no universally accepted definition of health-related quality of life (HRQOL), there is a general consensus on the multidimensional aspect of this concept, which takes into account several factors including physical, emotional, social and cognitive functioning as well as disease symptoms [1–3]. HRQOL is now considered an important endpoint, particularly in cancer clinical trials, together with the traditional clinical endpoints. HRQOL assessment is particularly valuable in trials where survival benefits are expected to be small [4–6]. Increasingly, over the last decade, many clinical trials have routinely incorporated HRQOL, usually as a secondary endpoint but occasionally as the primary endpoint [7]. Whilst the number of HRQOL studies in cancer research is increasing, there remains a compelling need for more evidence of the utility of HRQOL data for clinical practice [8]. In particular,

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doi:10.1016/j.ejca.2004.01.014

HRQOL studies that may help bridge the gap between research and clinical practice are particularly important for clinicians.

Breast cancer is the most common cancer in women in the Western world [9] and metastatic breast carcinoma is largely incurable [10]. Hence, HRQOL issues are especially important when trying to weigh the clinical benefits of a possible treatment for breast cancer. Prognostic factors are sought in cancer research to identify variables that are independent predictors of outcome. This can help to stratify patients in the design and analyses of clinical trials and also assists in the interpretation of trial outcomes. Moreover, prognostic factors aid the clinical management of individual cancer patients, identifying for example those most likely to benefit from a specific intervention.

Previous studies of patients with advanced or metastatic breast cancer have shown HRQOL data to be predictors of primary clinical outcomes. Coates and colleagues [11] showed that good physical well-being was an independent predictor of survival. Likewise, Kramer and colleagues [12] showed that patient-reported pain scores were an independent prognostic factor for survival. Pretreatment HRQOL scores also correlate with survival in other tumour types including lung cancer [13–15], colorectal cancer [16,17], multiple myeloma [18], melanoma [19] and in a mixed population of cancer patients [20,21].

Particularly in metastatic disease, the recent literature seems largely supportive of the independent value of HRQOL parameters in predicting survival. Given the sometimes conflicting results arising from different studies, it is still difficult to draw firm conclusions on the nature of the underlying mechanism, and different explanations can be given [22]. The potential benefits of this line of research for clinical practice have also been previously highlighted [23]. However, caution is required when evaluating results from these studies. Part of the difficulty of interpreting prognostic-factor analyses of HRQOL parameters arises from the self-assessment questionnaires themselves, in which individual items or subscales may be highly correlated [24].

In this research we report an exploratory analysis of baseline clinical and HRQOL data as factors prognostic for survival from a randomised, controlled trial (RCT) comparing doxorubicin and paclitaxel with doxorubicin and cylophosphamide as first-line chemotherapy in 275 patients with metastatic breast cancer.

2. Patients and methods

2.1. Treatment and trial design

The European Organisation for Research and Treatment of Cancer (EORTC) trial 10961 was a multicentre study of 275 patients with metastatic breast cancer. Patients were centrally randomised at the EORTC Data Centre in Brussels after stratification for centre, prior chemotherapy (none versus adjuvant), performance status (ECOG 0 versus 1 and 2) and presence of bone metastases (yes versus no). Patients received either AT (doxorubicin 60 mg/m^2 plus paclitaxel 175 mg/m^2 as an infusion over 3 h) or AC (doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2). Treatment was given every 3 weeks for a maximum of six cycles. Full details have been reported by Biganzoli and colleagues [10].

The trial, approved by the EORTC protocol review committee and the ethics committee of each participating centre, was conducted in compliance with the Helsinki declaration. All patients provided written informed consent.

2.2. Patients

To be eligible, patients were required to be female with histologically or cytologically proven breast cancer, who had metastatic disease and uni- or bidimensionally measurable lesions and had not previously been treated with chemotherapy for metastatic disease. Other eligibility requirements were ECOG performance status of 0 to 2, and a life expectancy of at least 12 weeks. Exclusion criteria included symptomatic brain metastases and bone metastases as the only site of disease.

2.3. Methods of HRQOL evaluation

Two HRQOL measures were selected, the EORTC QLQ-C30 (version 2.0) [25] and the QLQ-BR23 Breast module [26], because of their robust psychometric properties resulting from widespread use in international cancer clinical trials [27–29]. The EORTC QLQ-C30 is a core measure designed to be supplemented with the disease specific QLQ-BR23, developed and validated in patients with breast cancer. Both instruments were available in the language of all participating patients (in translation), following EORTC procedures [30].

The EORTC QLQ-C30 comprises five function scales: physical (PF), role (RF), emotional (EF), cognitive (CF) and social (SF); three symptom scales: fatigue (FA), nausea/vomiting (NV), and pain (PA); six single-item scales: dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhoea (DI) and financial difficulties (FI); and a global health-status scale (QL).

The EORTC Breast Cancer Module (EORTC QLQ-BR23) is designed for use with patients with different stages of disease and treatment modality (surgery, chemotherapy, radiotherapy and hormonal treatment). The module incorporates 23 questions grouped into five multi-item scales to assess systemic therapy side-effects (BRST), arm symptoms (BRAS), breast symptoms

(BRBS), body image (BRBI), and sexual functioning (BRSEF). Sexual enjoyment (BRSEE), upset by hair loss (BRHL) and future perspectives (BRFU) are assessed as single items. Assessments were performed at baseline or just after randomisation but before treatment.

To maximise compliance and minimise error variance due to uncontrolled differences in the timing or other external aspects of the assessments, HRQOL data collection was an integral part of the clinical trial [31]. Wherever possible, the questionnaires were administered at the clinic in a room where the patient would not be disturbed. The protocol specified that a responsible nurse, clinician or data manager administer the questionnaire to the patient requesting its completion and returning it to the data centre. EORTC guidelines for administering questionnaires were provided ensuring a standard approach to the collection of HRQOL data.

2.4. Variables examined

All the HRQOL variables from the EORTC QLQ-C30, with the exception of constipation, diarrhoea and financial difficulties were studied. We also preselected certain variables from the EORTC QLQ-BR23 for this analysis, namely systemic therapy side-effects and future perspective, as they were thought possibly to impact on predicting survival. The items on both measures were scaled and scored using the recommended EORTC procedures [32]. These involved transformation of raw scores to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. In the case of missing items within a scale, the scale score was calculated using only those for which values were available, provided at least half of the items in the scale were completed. We also analysed clinical factors: age, performance status, bone metastases, dominant site of disease, number of sites involved, disease-free interval as well as oestrogen and progesterone receptors.

2.5. Statistical considerations

The primary endpoint for the trial was progression-free survival; secondary endpoints were response rate, safety, survival, and quality of life. The planned sample size of 260 patients was based on the primary endpoint.

Survival curves and probabilities were estimated using the Kaplan–Meier technique [33]. Differences between survival curves were assessed using the log-rank test. [34]. The Cox proportional-hazards regression model [35] was used for both univariate and multivariate analyses of survival. For the analysis of prognostic factors for survival analysis, the proportionality assumption was checked for each of the variables under study by testing the dependency of their hazard ratio over time [36]. All univariate analyses were stratified for treatment. Treatment was also included as a covariate in the starting model for the multivariate analyses, along with all the covariates from the univariate analyses. The HRQOL scales described above were all included as continuous factors, using data from baseline assessment. A stepwise (back and forward) variable selection procedure was used to identify independent factors prognostic for survival. The importance of a prognostic factor was assessed using the P-value of the Wald statistic, the hazard ratio and its 95% Confidence Interval (CI) for survival. A level of 1% of significance was used for both clinical and patient-assessed HRQOL variables to reduce the risk of false-positive results arising from multiple testing. All significance tests were two-sided. Pearson's correlation coefficients were used to investigate the association between different covariates. Data analysis was performed using *Statistical Analysis Software* (SAS) version 8.02 [37].

3. Results

Between November 1996 and February 1999, 275 patients from 24 institutions were randomised to receive AT (138) or AC (137). Of these patients, 114 randomised to AT (82.6%) and 105 randomised to AC (76.6%) had baseline HRQOL measures completed and were included in this analysis. Characteristics of all the patients enrolled in the trial were compared with those for whom HRQOL data were available at baseline. Overall, patients' characteristics with or without baseline scores were well balanced, with no significant differences between groups (Table 1). Although the patients without baseline evaluation had slightly worse performance status, this was not significant ($P=0.502$). Baseline HRQOL scores are shown in Table 2. Taking into account all patients, with or without HRQOL data, median progression-free survival was 6 months in both treatment arms. The response rates were 58% and 54%, with a median overall survival of 20.6 versus 20.5 months in the AT and AC arms, respectively. All the following analyses are based only on the 219 patients having HRQOL baseline data.

3.1. Univariate analysis of survival

The clinical variables that were related to poor survival were low performance status ($P<0.001$; Fig. 1), increased number of sites involved ($P=0.001$) and multiple sites of visceral disease ($P=0.014$). Three functioning (physical, social and role) scales as well as symptoms (pain, fatigue, dyspnoea and appetite loss) were predictors of survival at $P<0.01$. A borderline difference was also found for systemic therapy side-effects as measured by the EORTC QLQ-BR23 ($P=0.019$). No other HRQOL or clinical variables were

significantly predictive of survival. Detailed results are given in Table 3. The four strongest HRQOL variables affecting survival, based on their *P*-values, (appetite loss, physical and role functioning as well as fatigue) were dichotomised according to their observed mean scores and curves are presented in Figs 2–5, respectively.

3.2. Multivariate analysis of survival

The full multivariate model contained 10 clinical factors, 14 HRQOL scales and treatment indicator as covariates. After stepwise selection, the final model retained one clinical variable and one HRQOL variable as independent prognostic factors: performance status and appetite loss (see Table 4). Higher values for these variables were associated with shorter survival.

In order to evaluate the association between appetite loss and the other HRQOL variables that were significant in the univariate analyses, a Pearson correlation matrix for these variables was also performed. The variables most strongly correlated with appetite loss were role and physical functioning, as well as fatigue ($|r| > 0.5$). Global health status and nausea/vomiting also showed considerable correlation ($|r| > 0.4$). Results are reported in Table 5.

Table 1
Patient characteristics: difference between patients with and without health-related quality-of-life baseline assessment

Variables	Baseline	
	Without ($N=56$) N (%)	With ($N=219$) N (%)
Age		
Median	51.5	53
Range	28 67	28 70
Number of observations	56	219
Performance status		
Normal	20 (35.7)	99 (45.2)
Slightly symptomatic	30 (53.6)	103 (47.0)
Symptomatic, <50% in bed	5 (8.9)	17 (7.8)
Unknown	1 (1.8)	0 (0.0)
Bone metastases		
No	25 (44.6)	95 (43.4)
Yes	25 (44.6)	106 (48.4)
Unknown	6 (10.7)	18 (8.2)
Oestrogen receptor (most recent value)		
Negative	22 (39.3)	74 (33.8)
Positive	19 (33.9)	84 (38.4)
Unknown	15 (26.8)	61 (27.9)
Progesterone receptor (most recent value)		
Negative	19 (33.9)	79 (36.1)
Positive	14 (25.0)	65 (29.7)
Unknown	23 (41.1)	75 (34.2)
Dominant site		
Unknown	10 (17.9)	8 (3.7)
Soft tissue	9 (16.1)	17 (7.8)
Bone	3 (5.4)	19 (8.7)
Single visceral	23 (41.1)	118 (53.9)
Multiple visceral	11 (19.6)	57 (26.0)
Number of sites involved		
Unknown	10 (17.9)	8 (3.7)
1	14 (25.0)	51 (23.3)
2	15 (26.8)	81 (37.0)
3	12 (21.4)	57 (26.0)
more than 3	5 (8.9)	22 (10.0)
Disease-free interval (months)		
Median	30	35.8
Range	0 218.1	0 355.3
Number of observations	47	186

4. Discussion

This study suggests that in addition to clinical variables, selected baseline HRQOL variables might significantly predict survival in women with metastatic breast cancer. Patient characteristics of those with or without HRQOL data at baseline were very similar, so the women in our study seem representative of the overall trial population.

All the main clinical factors were examined in the univariate analyses (Table 3), and of these, performance

Table 2
Baseline health-related quality-of-life scores

EORTC QLQ-C30	
Functional scales	
Physical functioning (PF)	70.1±26[a]
Emotional functioning (EF)	58.9±25
Cognitive functioning (CF)	81.6±21
Social functioning (SF)	72.5±29
Role functioning (RF)	63.7±32
Global health status (QL)	56.4±24
Symptom scales	
Fatigue (FA)	38.3±26
Pain (PA)	32.6±32
Nausea and Vomiting (NV)	9.5±17
Dyspnoea (DY)	26.3±31
Insomnia (SL)	37.8±33
Appetite loss (AP)	22±29
Constipation (CO)	15.6±26
Diarrhea (DI)	9.3±19
Financial difficulties (FI)	14.53±25
EORTC QLQ-BR23	
Functional scales	
Body image (BRBI)	78.6±24
Sexual functioning (BRSEF)	17±22
Sexual enjoyment (BRSEE)	55.5±32
Future perspective (BRFU)	32.5±33
Symptom scales	
Systemic therapy side-effects (BRST)	16.7±13
Breast symptoms (BRBS)	16.4±19
Arm symptoms (BRAS)	21.3±24
Upset by hair loss (BRHL)	40.47±34

[a] Values are given as mean±SD.

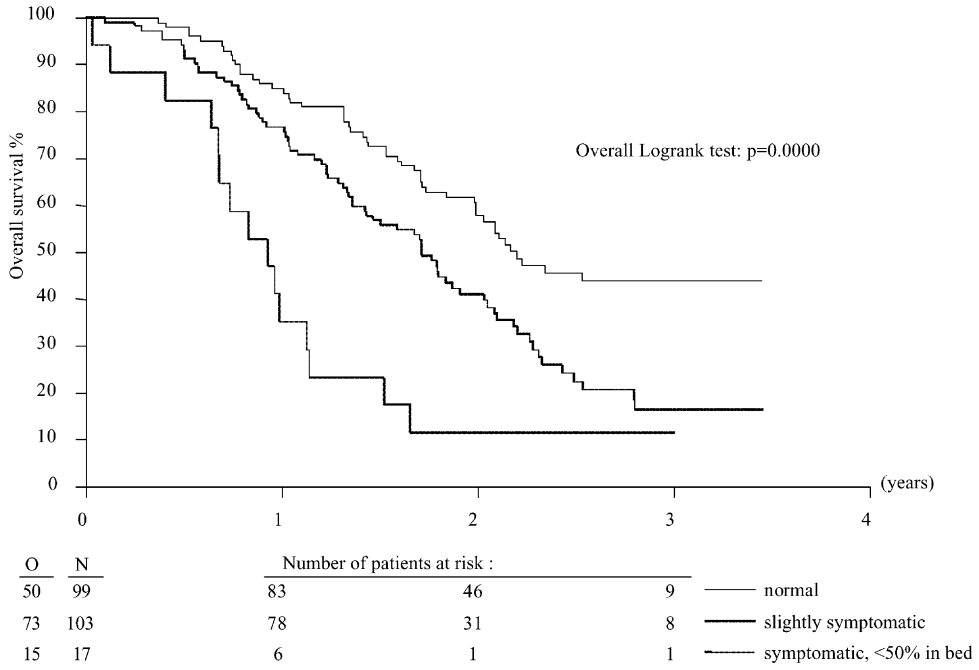

Fig. 1. Duration of survival by performance status. O, observed number of deaths; N, number of patients.

Table 3
Univariate prognostic-factor analyses of survival

Variables	Hazard ratio	95% (CI)	*P*
Clinical			
Age	0.999	0.981–1.017	0.887
Performance status	1.989	1.510–2.619	<0.001
Bone metastases	1.179	0.825–1.684	0.366
Dominant site of disease:			
Soft versus bone	1.370	0.507–3.705	0.535
Soft versus single visceral	2.039	0.938–4.432	0.072
Soft versus multiple visceral	2.749	1.224–6.175	0.014
Number of sites involved	1.349	1.126–1.617	0.001
Oestrogen receptor	0.867	0.572–1.316	0.503
Progesterone receptor	0.890	0.578–1.371	0.598
Disease-free interval	0.996	0.992–1.000	0.064
EORTC QLQ-C30			
Physical functioning	0.986	0.980–0.992	<0.001
Emotional functioning	0.998	0.992–1.005	0.626
Cognitive functioning	0.994	0.986–1.001	0.108
Social functioning	0.992	0.987–0.998	0.009
Role functioning	0.990	0.985–0.995	<0.001
Global health status	0.993	0.986–0.999	0.032
Pain	1.007	1.002–1.012	0.006
Fatigue	1.012	1.006–1.019	<0.001
Nausea and vomiting	1.011	1.001–1.020	0.023
Dyspnoea	1.007	1.002–1.012	0.007
Insomnia	1.003	0.998–1.009	0.247
Appetite loss	1.011	1.006–1.017	<0.001
EORTC QLQ-BR23			
Systemic therapy side-effects	1.015	1.002–1.028	0.019
Future perspective	0.999	0.993–1.004	0.579

status (Fig. 1) was retained in the final multivariate model as a strong predictor of survival (Table 4). This finding is consistent with past studies. Some studies in patients with advanced breast cancer have also found the oestrogen and progesterone receptor status of the primary tumour to be significant prognostic factors for survival [38–40]. Generally, however, these variables were not retained in the final multivariate model when including other clinical factors such as disease-free interval and dominant site of disease [40]. Kramer and colleagues [12] used several clinical variables in their prognostic analyses of patients with advanced breast cancer and found disease-free interval and multiple sites of visceral disease to be the strongest predictors of survival. These findings differ from our own, which identified performance status as the strongest predictor of survival in the final multivariate analyses (Table 4). It is worthy of note, however, that the earlier study was

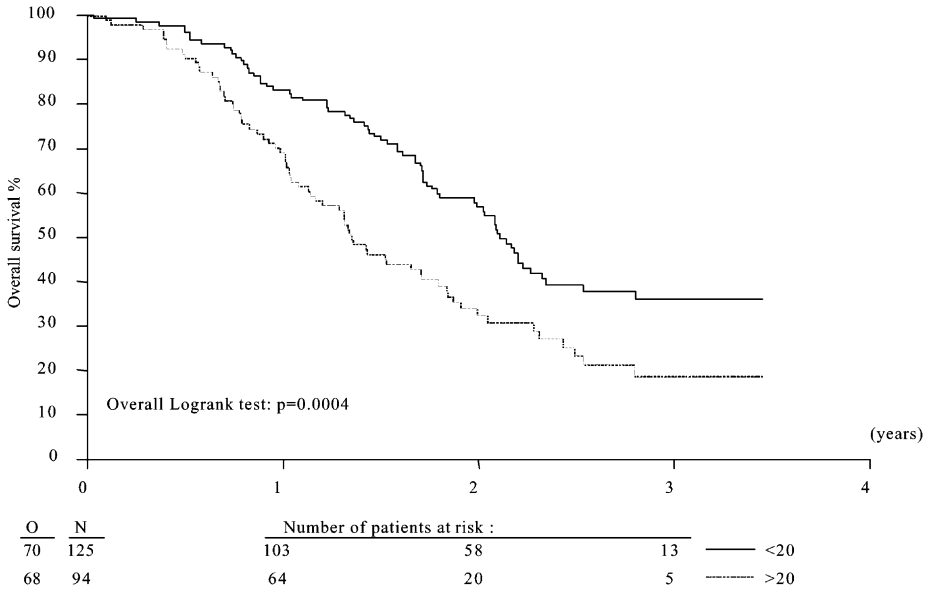

Fig. 2. Duration of survival by EORTC QLQ-C30 appetite loss score (<20 versus >20). O, observed number of deaths; N, number of patients. A high score on appetite loss represents worse health-related quality of life.

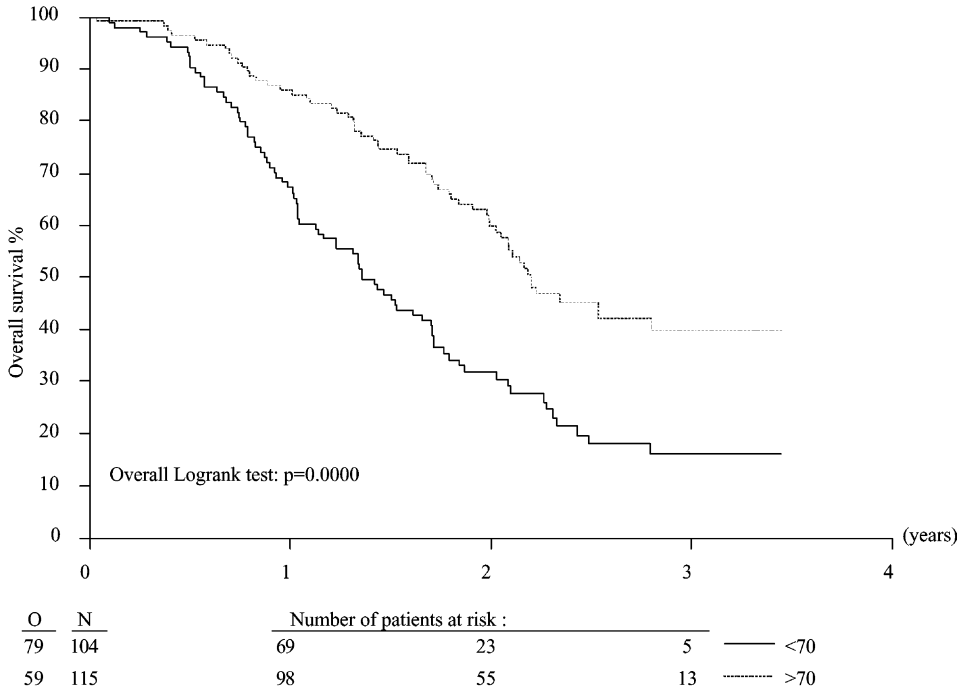

Fig. 3. Duration of survival by EORTC QLQ-C30 physical functioning score (<70 versus >70). O, observed number of deaths; N, number of patients. A high score on physical functioning represents high health-related quality of life.

restricted to patients with favourable performance status, so limiting the influence of this variable as a prognostic factor. Overall, our results are consistent with previous studies confirming clinical factors such as performance status as important prognostic factors for survival in women with advanced breast cancer [41–43].

In the univariate analyses the following HRQOL variables were significantly related to survival ($P<0.01$): physical, social and role functioning scales as well as pain, fatigue, dyspnoea and appetite loss (Table 3). All these variables were entered simultaneously, in a stepwise procedure. During this procedure, the final model retained, as an independent prognostic factor, the HRQOL variable appetite loss ($P=0.005$).

Previous studies, using the EORTC QLQ-C30, have also found HRQOL variables to be independent prognostic factors predicting survival in multivariate analyses. Global quality of life was one of the variables

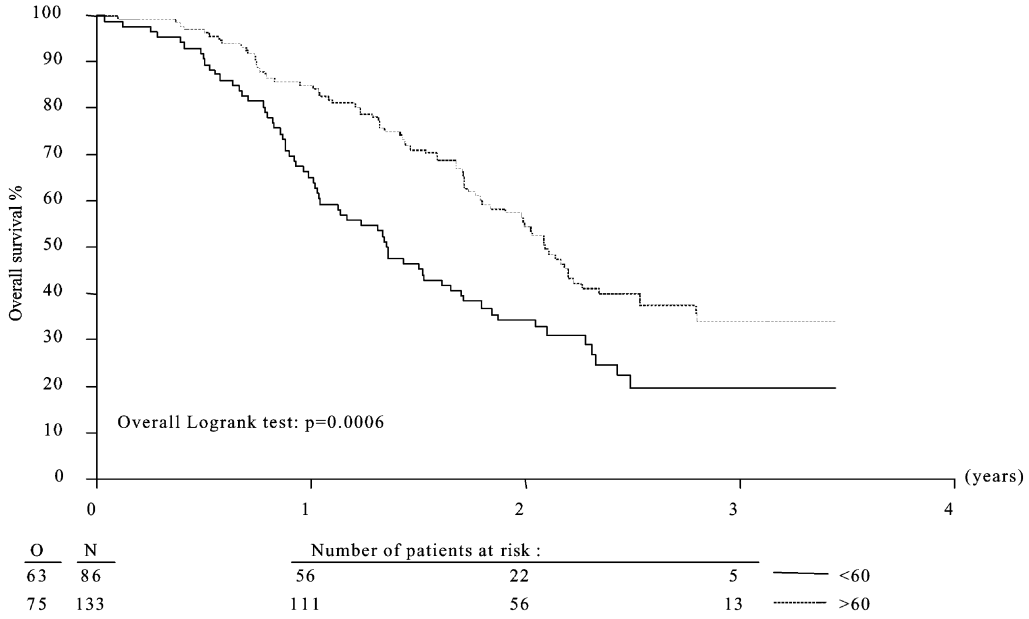

Fig. 4. Duration of survival by EORTC QLQ-C30 role functioning score (<60 versus >60). O, observed number of deaths; N, number of patients. A high score on role functioning represents high health-related quality of life.

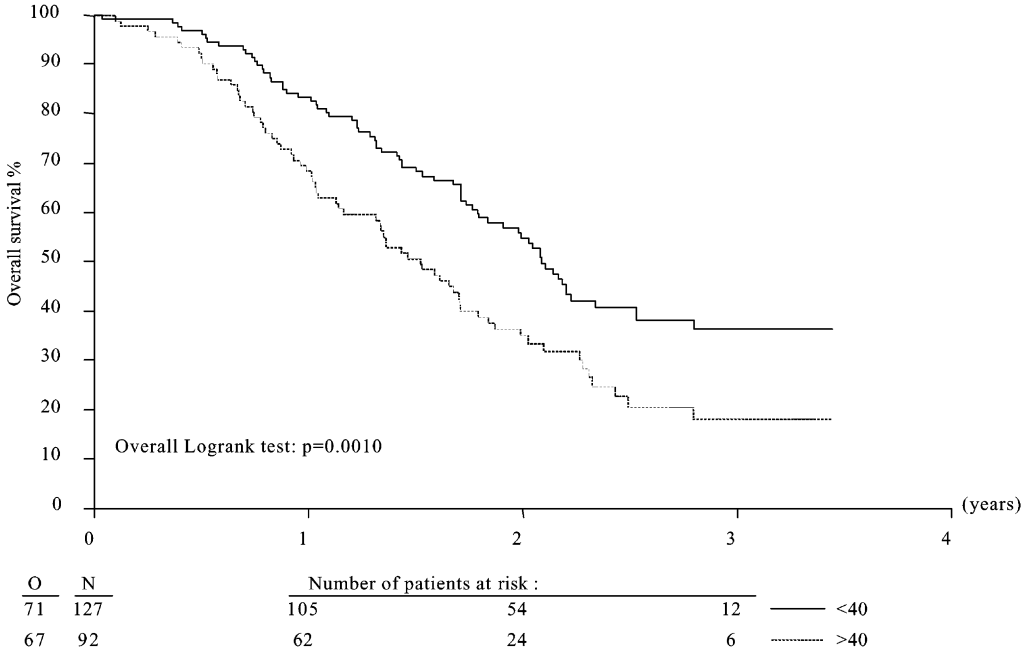

Fig. 5. Duration of survival by EORTC QLQ-C30 fatigue score (<40 versus >40). O, observed number of deaths; N, number of patients. A high score on fatigue represents worse health-related quality of life.

Table 4
Final multivariate model

Variables	Hazard ratio	95% (CI)	P
Appetite loss	1.008	1.002–1.013	0.005
Performance status	1.778	1.340–2.359	<0.001

Table 5
Pearson correlation matrix between health-related quality-of-life (HRQOL) variables and appetite loss

HRQOL variables	Appetite loss
Global health status	−0.46099
Fatigue	0.53928
Nausea/vomiting	0.45220
Pain	0.33373
Dyspnoea	0.31978
Insomnia	0.35241
Role functioning	−0.55337
Physical functioning	−0.51810
Social functioning	−0.35337
Emotional functioning	−0.19366
Cognitive functioning	−0.21826
Systemic therapy side-effects	0.35093
Future perspective	−0.14217

most often associated with survival [17,21,44]. In our study this variable was not an important factor either in the univariate analyses or the multivariate model. Other HRQOL variables of the EORTC QLQ-C30 were, however, independent prognostic factors, such as physical functioning for patients with bladder [45] and oesophageal [46] cancer, and cognitive functioning for those with head and neck cancer [47]. Specifically for patients with advanced breast cancer, previous research using the EORTC QLQ-C30 found HRQOL variables to be independent prognostic factors in the final multivariate model. Kramer and colleagues [12] and Luoma and colleagues [48] identified pain as the strongest variable predicting survival. This is partly consistent with our findings, as pain was significant only in the univariate analyses. In our final model, appetite appeared as the strongest independent HRQOL prognostic factor; better appetite, in fact, was associated with longer survival (Fig. 2). Our result is consistent with previous research in metastatic breast cancer, which highlighted better appetite as a strong prognostic factor for survival [49]. Item non-response for this variable was negligible, being 1 out of 219 patients.

The relation between appetite loss and survival is not immediately clear and warrants further investigation; perhaps it might act as a mediating variable in patients with advanced disease. We constructed a correlation matrix in order to evaluate other HRQOL variables strongly associated with appetite loss (Table 5). The three strongest variables associated with appetite loss were role and physical functioning as well as fatigue ($|r| > 0.5$). The survival curves for these variables (Figs 2–5) all showed significant effects as measured by the log-rank test. Of these four HRQOL variables (appetite loss, fatigue, role and physical functioning), appetite loss seems to have the least clear clinical interpretation. Why then, if these four scales are so closely related to each other, is appetite loss retained in the final model? A possible answer is the correlation between HRQOL factors and performance status. Of the HRQOL factors, appetite loss is the one least associated with performance status. Hence in the final model, appetite loss emerges as the best HRQOL factor because there was less overlap with performance status than for fatigue, role and physical functioning. For this reason, attention has to be paid to the multicollinearity of the subscales when interpreting outcomes, especially with the EORTC QLQ-C30 [24]. Yet, whereas there is a general agreement on the value of HRQOL data as prognostic factors predicting survival (mainly in metastatic disease), results coming from these studies often identify different HRQOL variables predicting survival. Hence, better insights for future prognostic-factor analyses of HRQOL data might be achieved by using different statistical approaches checking for sensitivity and robustness of the results, e.g. a model-averaging technique, based on repeated forward Cox PH model building on bootstrap-generated data-sets, could be applied to investigate both the stability and the magnitude of the included HRQOL factors [24,50].

In conclusion, our findings suggest that appetite loss may be an important predictor of survival in addition to the well-recognised clinical factors. However, more work is required in this area and caution is necessary when interpreting results. Further studies are also needed to address the issue of multicollinearity inherently present between HRQOL questionnaire subscales, and shed more light on the clinical value of these outcomes.

Acknowledgements

Fabio Efficace was supported by the Camilla Samuel Fellowship in memory of Lady Grierson. The clinical trial was supported by a grant from Bristol–Myers Squibb. The authors wish to thank Sheila Sanderson Scott for the review of the manuscript.

Appendix

The following investigators and their institutions also participated in the study: B. Rapoport, The Medical Oncology Center, Johannesburg, South Africa; M. Nooij, LUMC, Leiden, the Netherlands; P. Ellis, Guy's Hospital, London, United Kingdom; A. Sulkes, Beilinson

Medical Center, Petach Tikva, Israel; H. Curé, Centre Jean Perrin, Clermont Ferrand, France; C. Mendiola, Hospital Universitario 12 de Octubre, Madrid, Spain; D. Spaeth, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France; R. Morant, Kantonsspital, St Gallen, Switzerland; J.P. Guastalla, Centre Léon Bérard, Lyon, France; C. Dittrich, Kaiser Franz Josef-Spital, Vienna, Austria; L. Beex, Universitair Ziekenhuis Nijmegen, Nijmegen, the Netherlands; L. Mauriac, Fondation Bergonié, Bordeaux, France; K.J. Roozendaal, Onze Lieve Vrouw Gasthuis, Amsterdam, The Netherlands; T. Velu, Hôpital Erasme, Brussels, Belgium; and M. Aapro, European Institute of Oncology, Milan, Italy.

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