Original Article

Quality of Life as a Prognostic Indicator of Survival: A Pooled Analysis of Individual Patient Data From Canadian Cancer Trials Group Clinical Trials

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BACKGROUND: The aims of this study were to externally validate an established association between baseline health-related quality of life (HRQOL) scores and survival and to assess the added prognostic value of HRQOL with respect to demographic and clinical indicators. **METHODS:** Pooled data were analyzed from 17 randomized controlled trials opened by the Canadian Cancer Trials Group between 1991 and 2004; they included survival and baseline HRQOL data from 3606 patients with 8 different cancer sites. The models included sex, age (≤60 vs >60 years), World Health Organization performance status (0 or 1 vs 2-4), distant metastases (no vs yes), and 15 European Organization for Research and Treatment of Cancer (EORTC) Core Quality-of-Life Questionnaire (QLQ-C30) scales. Analyses were conducted with multivariate Cox proportional hazards models and were stratified by cancer site. Harrell's discrimination C-index was used to calculate the predictive accuracy of the model when HRQOL parameters were added to clinical and demographic variables. The added value of adding HRQOL scales to clinical and demographic variables was illustrated with Kaplan-Meier curves. **RESULTS:** In the stratified, multivariate model, HRQOL parameters—global health status (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.95-1.00; $P < .0001$), dyspnea (HR, 1.04; 95% CI, 1.02-1.06; $P < .0002$), and appetite loss (HR, 1.06; 95% CI, 1.04-1.08; $P < .0001$)—were independent prognostic factors in addition to the demographic and clinical variables (all P values $< .05$). Adding these HRQOL variables to the clinical variables resulted in an added relative prognostic value for survival of 5%. **CONCLUSIONS:** These results confirm previous findings showing that baseline HRQOL scores on the EORTC QLQ-C30 provide prognostic information in addition to information from clinical measures. However, the impact of specific domains may differ across studies. ***Cancer*** **2018;124:3409-16.** *© 2018 American Cancer Society.*

KEYWORDS: cancer clinical trial, health-related quality of life, overall survival, pooled analysis, prognostic factor.

INTRODUCTION

In past decades, the outcomes of medical treatments have been measured primarily in terms of overall survival (OS), disability, or cure. In recent years, however, health-related quality of life (HRQOL) has increasingly been recognized as an important additional outcome measure in clinical decision making,[1-4] particularly in the setting of advanced disease.[5,6] This is reflected in the increased use of HRQOL assessments in randomized controlled trials in cancer over time.[4,7]

The incorporation of HRQOL in addition to clinical data might also improve survival prediction for patients with cancer. Gotay et al[8] demonstrated that there is a significant association between patient HRQOL and OS. In 36 of the 39

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studies reviewed, at least 1 HRQOL scale was significantly associated with survival in a multivariate analysis controlling for major clinical variables. The relative prognostic strength of different scales, however, varied across cancer sites.[9]

In a pooled analysis including HRQOL data from 7417 cancer patients, Quinten et al[7] showed that several HRQOL scales (physical functioning, pain, and appetite loss) were prognostic for OS independently of the particular cancer site. In addition, these HRQOL variables were found to increase prognostic accuracy by 6% in comparison with demographic and clinical variables only (age, sex, World Health Organization [WHO] performance status [PS], and distance metastases). The aim of the current pooled analysis is to externally validate the results of Quinten et al's study in a large and diverse sample of cancer patients from Canada. This pooled meta-analysis represents the largest data set that has been analyzed to assess the prognostic value of HRQOL data, and it is surpassed only by the original study that we are replicating.[7] Also, with the current replication crisis in the psychosocial literature, the National Institutes of Health and other bodies have emphasized the importance of such confirmation of important principles underlying how we think about psychological and medical concepts. Our design and results should, therefore, be evaluated in this context. Thus, the goals of this study are to confirm the association between baseline HRQOL scores on the European Organization for Research and Treatment of Cancer (EORTC) Core Quality-of-Life Questionnaire (QLQ-C30) and survival and to assess the added prognostic value of HRQOL with respect to clinical variables independent of the cancer site.

MATERIALS AND METHODS

We merged baseline HRQOL data from 17 closed randomized controlled phase 3 trials opened by the Canadian Cancer Trials Group (CCTG) between 1991 and 2004. When these trials were selected from our overall database,[10] trials that had cancer sites with very few patients ($\leq$10), unspecified cancer types, no events, or nonstandard modification of the EORTC QLQ-C30 were excluded to facilitate the modeling; this left 8 types of cancer and 3606 patients (from 4637 Canadian trial patients in the database overall). The 8 retained cancers were breast cancer, cervical cancer, ovarian cancer, colorectal cancer, head and neck cancer, myeloma, non–small cell lung cancer, and small cell lung cancer. HRQOL was assessed as a secondary outcome in all but 1 of the CCTG trials, in which it was the primary outcome. Baseline HRQOL data were available for all patients because completion of the baseline HRQOL assessment was an eligibility criterion in each of these studies.

Data Collection

HRQOL was assessed with the EORTC QLQ-C30.[11,12] The EORTC QLQ-C30 is a well-validated and accepted instrument for measuring various HRQOL domains. The QLQ-C30 contains both single- and multi-item scales. Of the 30 items, 24 aggregate into 9 multi-item scales representing various HRQOL dimensions: 5 functioning scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, pain, and nausea), and 1 global measure of health status. The remaining 6 single-item scales assess symptoms: dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and the perceived financial impact of the disease and treatment.[11] All scale and item scores are linearly transformed into a scale ranging from 0 to 100 for ease of statistical interpretation and psychometric validation. High scores indicate better HRQOL for the 5 functional scales and the global measure of health status but worse HRQOL for the symptom scales and items.[12] All scales and single items meet the standards for reliability. EORTC scoring and analysis guidelines and CCTG standardized procedures for administration and data management were used for every trial. Versions 1 and 3 of the EORTC QLQ-C30 were used in the MA16, MA8, CX2, HN1, HN2, MY7, SC15, BR8, SC8, and SC19 trials and were scored accordingly. The remaining trials—CO10, CO7, CO9, BR10, BR9, OV10, and SC11—used a modified version of the EORTC QLQ-C30 that could be converted into an established version. Additional assessed data included age, sex, WHO PS, distant metastases, and cancer sites. The age and WHO PS variables were dichotomized. The cutoff point for age was chosen to be 60 years on the basis of the previous study[7] and the United Nations–agreed cutoff for an "older population."[13] The WHO PS was dichotomized as a score of 0 or 1 (good) or a score of 2 to 4 (poor). All patients provided written informed consent, and all original studies as well as this meta-analysis project received appropriate ethics approval.

Statistical Analysis

The Cox proportional hazards model (CPHM) was used for the analysis.[14] The outcome variable was OS, which was measured from the date of randomization until the date of death (from any cause) and was calculated with the Kaplan-Meier method. Spearman rank correlation was used to investigate the relation between studied variables. The prognostic value of individual clinical and HRQOL

TABLE 1. Baseline Patient Characteristics by Cancer Type and Overall

Characteristic	Breast (n = 831)	NSCLC (n = 748)	Myeloma (n = 595)	Ovarian (n = 388)	Colorectal (n = 329)	Cervix (n = 272)	Head and Neck (n = 223)	SCLC (n = 220)	Total (n = 3606)
Age, mean (SD), y	51.37 (10.58)	63.09 (10.26)	70.67 (8.11)	56.68 (10.67)	63.82 (8.74)	47.44 (11.47)	58.18 (11.61)	57.65 (7.64)	58.93 (12.43)
Age, median (range), y	50.40 (54.80)	63.50 (55.40)	71.25 (52.10)	58.50 (55.80)	64.30 (44.10)	46.20 (49.60)	58.58 (66.44)	59.30 (37.20)	59.9 (75.22)
Age, No. (%)									
≤60 y	650 (78.22)	276 (36.90)	62 (10.42)	216 (55.67)	37 (11.25)	232 (85.29)	125 (56.05)	118 (53.64)	1716 (47.59)
>60	181 (21.78)	470 (62.83)	532 (89.41)	172 (44.33)	84 (25.53)	40 (14.71)	98 (43.95)	102 (46.36)	1678 (46.56)
Unknown	—	2 (0.27)	1 (0.17)	—	208 (63.22)	—	—	—	211 (5.85)
Sex, No. (%)									
Female	830 (99.88)	261 (34.89)	260 (43.62)	387 (99.74)	60 (18.24)	272 (100.00)	51 (22.87)	74 (33.64)	2194 (60.84)
Male	1 (0.12)	486 (64.97)	335 (56.21)	—	111 (33.74)	—	172 (77.13)	146 (66.36)	1251 (34.69)
Unknown	—	1 (0.13)	1 (0.17)	1 (0.26)	158 (48.02)	—	—	—	161 (4.46)
WHO PS, No. (%)									
0 or 1	736 (88.57)	631 (84.36)	366 (61.51)	317 (81.70)	117 (35.56)	265 (97.43)	206 (92.38)	197 (89.55)	2835 (78.62)
2 or 3	92 (11.07)	115 (15.37)	213 (35.80)	71 (18.30)	4 (1.22)	7 (2.57)	17 (7.62)	22 (10.00)	541 (15.0)
4	—	—	15 (2.52)	—	—	—	—	—	15 (0.42)
Unknown	3 (0.36)	2 (0.27)	1 (0.17)	—	208 (63.22)	7 (2.55)	—	1 (0.45)	215 (5.96)
Distant metastases, No. (%)									
Yes	646 (77.74)	76 (10.16)	—	161 (41.49)	50 (15.20)	8 (2.94)	31 (13.90)	220 (100.00)	1742 (48.31)
No	185 (22.26)	625 (83.56)	550 (92.44)	190 (48.97)	279 (84.80)	259 (95.22)	192 (86.10)		1730 (47.98)
Unknown	—	47 (6.28)	45 (7.56)	37 (9.54)	—	5 (1.84)	—	—	134 (3.72)

Abbreviations: NSCLC, non–small cell lung cancer; PS, performance status; SCLC, small cell lung cancer; SD, standard deviation; WHO, World Health Organization.

variables was evaluated with a univariate CPHM. Multivariate CPHMs were then used to evaluate the joint prognostic significance of variables that were shown to be univariably prognostic at the 5% level of significance. The cancer site was used as a stratification factor for both the univariate and multivariate models.

The model selection was performed in 2 steps. First, in the univariate model, each clinical and HRQOL variable was independently assessed with a criterion of $P < .05$. Second, the list of significant variables from the univariate analysis was implemented in a multivariate model, and stepwise selection was applied to eliminate nonsignificant parameters with a criterion of $P > .05$ in a multivariate framework. Stepwise procedures can reduce the problem of multicollinearity because 2 highly correlated predictors will normally not both be entered into the model.[15] The proportional hazards assumptions for both the univariate and multivariate analyses were assessed graphically with –log log survival probabilities for each factor in the model. Because of the large sample size, a formal goodness-of-fit test would have been overpowered.[16] As stated by Kleinbaum and Klein,[16] with a large sample size, even a small deviation from a proportional hazards assumption will result in a highly significant *P* value.

To assess the added value of the HRQOL scales, we ran and compared 2 stratified models. The first stratified multivariate model examined the prognostic value of the clinical variables only, and the second stratified multivariate model examined the additional prognostic value of the HRQOL scales/items when they were corrected for clinical variables (age, sex, distant metastases, and WHO PS). The prognostic value was assessed via the hazard ratio (HR), its 95% confidence interval (CI), and the *P* value of the Wald chi-square statistic. The reported HRs of the HRQOL scales/items were rescaled such that every unit increase in the HR corresponded to a minimally important difference of 10 points.[17] The model was refitted 5000 times with the bootstrap resampling technique to investigate the potential influence of sample bias and multicollinearity on the results[18] and to confirm the stability and robustness of the final model.

To complement the analyses of the prognostic value of HRQOL data, we estimated the discrimination and the effect of adding HRQOL information to clinical data by assessing Harrell's discrimination C-index statistic ($0 \leq C \leq 1$)[19] with its corresponding Akaike information criterion (AIC) values. A smaller AIC implies a better model fit. The C-index estimates the proportion of all pairwise patient combinations from the sample data whose survival time can be ordered such that the patient with the highest predicted survival is the one who has actually survived longer (discrimination) in the observed data set.[20] The C-index is a probability of concordance between predicted and observed survival, with $C = 0.5$ for random predictions and $C = 1$ for a perfectly discriminating model. We ran and compared 3 multivariate models: a model with no variables (a null model), a model with the clinical variables, and a model with the clinical variables and the HRQOL variables from the multivariate model.

To illustrate the added value of adding these selected HRQOL scales (global health status, dyspnea, and appetite loss) to demographic and clinical variables, we constructed an indicator variable representing an example scenario with 3 of the 4 clinical variables: female patients aged 60 years or younger with a good WHO PS (0 or 1). The selected HRQOL scales were categorized into 4 groups on the basis of the mean scores: 1) 0, 2) >0 to ≤33.3, 3) >33.3 to ≤66.6, and 4) >66.6 (scale, 0-100) for multi-item scales and 1) 0, 2) 33.3, 3) 66.6, 4) 100 for single item scales. These categories were chosen on the basis of the interquartile range of the scores. Distant metastatic status was not included in the construction of this indicator variable because its inclusion resulted in categories with very small event rates that were inestimable.

TABLE 2. Univariate Analysis of Clinical and HRQOL Parameters

	Hazard Ratio (95% CI)	*P*
Clinical Variables		
Age (≤60 vs >60 y)	0.686 (0.617-0.763)	<.0001
Sex (female vs male)	0.857 (0.763-0.961)	.0086
WHO PS (good vs poor)	0.433 (0.383-0.490)	<.0001
Distant metastases (no vs yes)	0.368 (0.299-0.453)	<.0001
QLQ-C30 HRQOL variables		
Global QOL/health status	0.908 (0.890-0.927)	<.0001
Physical functioning	0.917 (0.90-0.935)	<.0001
Role functioning	0.959 (0.946-0.972)	<.0001
Emotional functioning	0.973 (0.954-0.993)	.0093
Social functioning	0.954 (0.939-0.969)	<.0001
Cognitive functioning	0.946 (0.926-0.965)	<.0001
Fatigue	1.090 (1.069-1.111)	<.0001
Nausea/vomiting	1.079 (1.052-1.107)	<.0001
Pain	1.043 (1.026-1.061)	<.0001
Dyspnea	1.079 (1.06-1.098)	<.0001
Insomnia	1.033 (1.016-1.05)	<.0001
Appetite loss	1.096 (1.079-1.113)	<.0001
Constipation	1.041 (1.025-1.058)	<.0001
Diarrhea	1.012 (0.985-1.04)	.3746
Financial difficulties	0.999 (0.998-1.001)	. 5580

Abbreviations: CI, confidence interval; HRQOL, health-related quality of life; PS, performance status; QLQ-C30, Core Quality-of-Life Questionnaire; QOL, quality of life; WHO, World Health Organization

TABLE 3. Multivariate Analysis of Clinical and HRQOL Parameters

	Cox Model for Demographic and Clinical Data		Cox Model For Demographic, Clinical, and HRQOL Data	
	Hazard Ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Demographic and clinical variables				
Age	0.884 (0.799-0.979)	.0183	0.709 (0.628-0.802)	<.0001
Sex	0.897 (0.813-0.990)	.0313	0.851 (0.742- 0.976)	.0206
WHO PS	0.554 (0.492-0.625)	<.0001	0.621 (0.539-0.716)	<.0001
Distant metastases	0.473 (0.424-0.527)	<.0001	0.354 (0.280-0.449)	<.0001
QLQ-C30 HRQOL variables				
Global QOL/health status			0.970 (0.945-0.996)	<.0001
Dyspnea			1.039 (1.019-1.060)	.0002
Appetite loss			1.057 (1.038-1.077)	<.0001

Abbreviations: CI, confidence interval; HRQOL, health-related quality of life; PS, performance status; QLQ-C30, Core Quality-of-Life Questionnaire; QOL, quality of life; WHO, World Health Organization

Subsequently, the results of this study were compared with the results of Quinten et al[7] by means of a descriptive comparison. All models were analyzed with SAS (version 9.3 or later; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Table 1 shows baseline patient characteristics overall and by cancer type. Overall, the mean age of the patients was 58.9 years (standard deviation, 12.4 years), and the majority were women (61%). More than 78% of the patients had a good WHO PS (0 or 1). Patients were being treated for locoregional or metastatic disease; in 48% of the patients, metastatic cancer was present.

Table 2 describes the results of the univariate Cox regression analysis of all clinical and HRQOL variables. Age, sex, WHO PS, and the presence of distant metastases were significantly associated with survival. Patients with a good PS and those without distant metastases had longer OS, patients 60 years old or younger had increased OS, and women had higher OS than men. All selected HRQOL scores were prognostic of survival except for diarrhea and financial difficulties. We detected no violations of the proportionality assumptions for the variables investigated. All the –log log survival probability curves were approximately parallel over time except for distant metastases. The crossing of the curve for distant metastases was due to a few patients with survival times of zero. When we ignored the distant metastases for these patients, the –log log survival curve became parallel over time. We also reran the final model; when the values for distant metastases for these patients were deleted, the results did not change. Also, as expected, the *P* values from the goodness of fit were driven by the sample size. All *P* values from the goodness-of-fit test were highly statistically significant even with a slight violation of the proportional hazards assumption. As a result, the formal test was overpowered and, therefore, of little value.

The first stratified Cox multivariate model for OS included only the demographic and clinical variables. All 4 variables were retained as strong prognostic indicators. The second multivariate model included the 4 parameters and 13 HRQOL scales/items (Table 2). As a result of the stepwise selection procedure, the model retained age, sex, WHO PS, distant metastases, and 3 of the HRQOL scales/items (global health status, dyspnea, and appetite loss). Table 3 shows the HRs for the significant HRQOL and clinical variables.

The results from Harrell's discrimination C-index showed that with the inclusion of only the demographic and clinical variables in the model, the predictive accuracy increased from 0.5 (the null model) to 0.64 (64%) with an AIC value of 18,131.64; this represented a relative gain of 28% (0.64 – 0.5/0.5). When the clinical variables and the 3 significant HRQOL variables were included in the model, the predictive accuracy increased to 0.66 (AIC, 14,735.05), and this represented a relative gain of 34% ((0.67 – 0.5)/0.5). Thus, adding the global health status, dyspnea, and appetite loss variables alongside a clinical model improved the absolute prognostic accuracy by 6% (34% – 28%).

The results illustrate the added prognostic value of adding the baseline global health status, dyspnea, and appetite loss to clinical variables and an efficient way of interpreting HRQOL scores in terms of survival. Figure 1 presents Kaplan-Meier curves and OS statistics according to the QLQ-C30 score for global health status. We noted a predicted median OS time of 16.5 months (95% CI, 7.75-69.62 months) for patients with the worst global health status (theoretically, the model predicted a score of 0 on a scale from 0 to 100); this increased to 36 months (95% CI, 28.45-48.23 months) for patients with a better

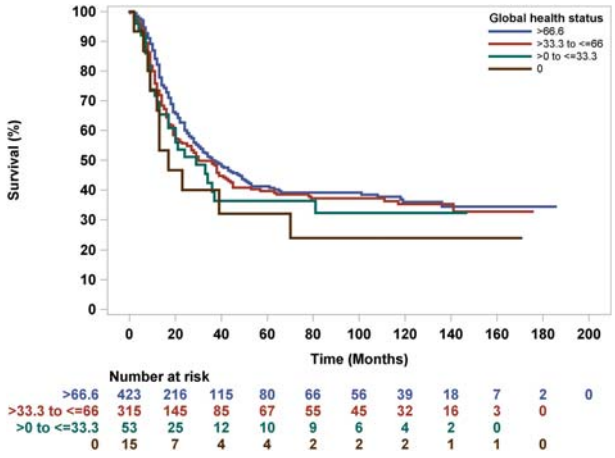

Figure 1. Overall survival curves stratified by the global health status (Core Quality-of-Life Questionnaire). CI indicates confidence interval.

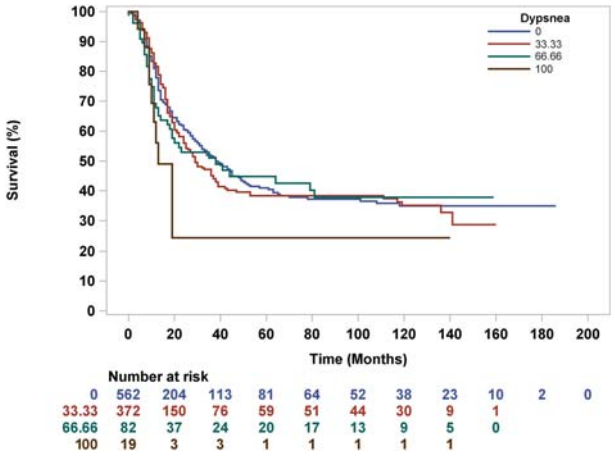

Figure 2. Overall survival curves stratified by dyspnea (Core Quality-of-Life Questionnaire). CI indicates confidence interval.

global health status (score > 66.6). Figure 2 presents Kaplan-Meier curves and OS statistics according to the QLQ-C30 score for dyspnea. We noted a predicted median OS time of 37.8 months (95% CI, 30.55-48.23 months) for patients with no dyspnea (theoretically, the model predicted a score of 0 on a scale from 0 to 100); this was reduced to 12.6 months (95% CI, 8.9-19.15 months) for patients with severe dyspnea (score = 100). Similar findings according to the QLQ-C30 score for appetite loss were observed. We noted a predicted median OS time of 38.1 months (95% CI, 31.51-61.08 months) for patients with no appetite loss (score = 0) versus 12.6 months (95% CI, 8.90-36.80 months) for patients with severe appetite loss (score = 100).

Lastly, to externally validate the results of Quinten et al,[7] we compared their results with those of the current study. In their study, the results showed that all clinical and HRQOL variables were significantly prognostic of OS in the univariate analyses, whereas we did not find prognostic significance for the diarrhea and financial difficulty scales. Furthermore, both studies found that appetite loss was an independent prognostic factor for OS in the multivariate approach. A difference was that Quinten et al also identified physical function and pain as independent prognostic factors of OS, whereas we additionally identified global health status and dyspnea. Nevertheless, both studies showed added prognostic value for HRQOL variables in addition to clinical variables: 5% in our study versus 6% in the study by Quinten et al.[7]

DISCUSSION

Our study has confirmed the additive prognostic value of HRQOL beyond clinical variables in a large, independent set of cancer patients. Several researchers have shown the prognostic value of various HRQOL scales. Beside Quinten et al,[7] Gotay et al[8] reported that global health status (in 15 of 39 studies reviewed) and physical function (in 11 of 39) each predicted survival more often than other HRQOL scales. Appetite loss (in 10 of 39 studies reviewed) frequently predicted survival, mainly in studies of patients with advanced metastatic disease, whereas dyspnea was a predictor of survival in 1 of 39 studies reviewed. Sloan et al[21] showed that overall HRQOL was a significant and independent prognostic factor for survival in patients with lung cancer. A pooled analysis by Qi et al[22] also showed that pretreatment HRQOL measured with the Uniscale (a single item assessing overall quality of life) was a significant independent prognostic factor for OS in non–small cell lung cancer. Individual studies and those focusing on a particular cancer site generally reported a higher HR for dyspnea[9,23] and appetite loss[9,24-26] than this pooled study, and this suggests that different HRQOL scales may have different prognostic importance for various cancer sites.

Similarly, the difference in independent prognostic factors between our study (global health status and dyspnea) and the study of Quinten et al[7] (physical function and pain) could possibly be explained by differences between the included studies with respect to sample size, cancer type, and disease stage. For example, Quinten et al included studies with more patients who were older (>60 years; 74% vs 48%) and had a worse performance status (WHO PS of 2 or 3, 80% vs 15%); their analysis also included more men (74% vs 35%) and different cancer sites. All associations between HRQOL and OS in the

multivariate analysis were in the expected direction: better HRQOL predicted better survival.

Moreover, a subset analysis of the same data set by Quinten et al[9] showed that the prognostic value of HRQOL differed for each cancer site. Physical function was significantly prognostic for melanoma, colorectal cancer, lung cancer, esophageal cancer, and breast cancer, whereas pain was significantly prognostic for colorectal cancer and lung cancer, appetite loss was significantly prognostic for colorectal cancer and prostate cancer, and dyspnea was significantly prognostic for head and neck cancer. Although there is some overlap, these results suggest that to be most valuable for predicting survival for an individual patient, HRQOL data should be analyzed separately for different cancer sites. Moreover, exploring the incorporation of baseline HRQOL into eligibility and/or stratification for cancer clinical trials (cancer-specific) and into clinical care is warranted.

Although the added absolute prognostic value of HRQOL is not very large (5% in this study), incorporating HRQOL measurements may be important for both cancer clinical practice and clinical trials. Several HRQOL scales have been found to be independent prognostic factors for survival and could, therefore, be used as stratification factors for future cancer clinical trials separately for different cancer sites. This would ensure that treatment groups are more comparable and enhance conclusions drawn about treatment efficacy.[8] It is not yet known whether intervening to improve HRQOL would improve survival. In clinical practice, both baseline HRQOL scores and sociodemographic and clinical variables should be taken into consideration when one is choosing and evaluating treatment. For example, for patients with poor HRQOL at the baseline, specific (supportive) treatments could be initiated to improve HRQOL. In addition, besides baseline data, regular HRQOL assessments during the course of treatment could be used to detect early deterioration of a patient; this could allow interventions to improve the patient's HRQOL to be implemented in a timely fashion.[27]

Our study is a secondary analysis and, therefore, has several limitations. Although we had a large sample of patients, we included a mixed population of cancer types. Quinten et al[9] showed that the prognostic value of HRQOL is heterogeneous across different cancer sites. Thus, additional HRQOL parameters may become prognostic or change in size or magnitude when they are studied for each cancer site separately. Besides the limited additional prognostic accuracy of HRQOL data, we should also note that the magnitudes of the HRs for the EORTC QLQ-C30 scales are in general smaller than those for the (categorized) clinical variables. Moreover, the HRQOL assessments in our study were limited to baseline observations only, and they yielded little variability in our predictors, which are designed to capture both disease and treatment effects. Another limitation of our study is the challenge of pooling data across groups of patients over a long time period; this is related to new versions and adaptations of questionnaires. This may induce variability during scoring of the questionnaires.

In conclusion, our findings validate previous findings showing that baseline HRQOL, as measured on subscales of the EORTC QLQ-C30, is prognostic for OS in cancer patients independently of the cancer type. Moreover, adding HRQOL variables to clinical variables improves prognostic accuracy. The accumulated results across many studies should now be seen as definitive. Future efforts to further determine to what extent these correlations are cancer type–specific, to assess why HRQOL ratings predict survival, and to determine how to use this information in interventions and clinical care are warranted.[28]

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CONFLICT OF INTEREST DISCLOSURES

Martin Taphoorn reports personal fees from Hoffmann–La Roche outside the submitted work.

AUTHOR CONTRIBUTIONS

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