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REVIEW ARTICLE

The Prognostic Significance of Patient-Reported Outcomes in Cancer Clinical Trials

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ABSTRACT

Purpose
Patient-reported outcomes (PROs), routinely collected as a part of cancer clinical trials, have been linked with survival in numerous clinical studies, but a comprehensive critical review has not been reported. This study systematically assessed the impact of PROs on patient survival after a cancer diagnosis within the context of clinical trials.

Design
Cancer clinical trials that assessed baseline PROs and mortality were identified through MEDLINE (through December 2006) supplemented by the Cochrane database, American Society of Clinical Oncology/European Society for Medical Oncology abstracts and hand searches. Inclusion criteria were publication in English language and use of multivariate analyses of PROs that controlled for one or more clinical factors. Two raters reviewed each study, abstracted data, and assessed study quality; two additional raters verified abstractions.

Results
In 36 of 39 studies (N = 13,874), at least one PRO was significantly associated with survival ($P < .05$) in multivariate analysis, with varying effect sizes. Studies of lung (n = 12) and breast cancer (n = 8) were most prevalent. The most commonly assessed PRO was quality of life, measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 in 56% of studies. Clinical variables adjusted for included performance status (PS), treatment arm, stage, weight loss, and serum markers. Results indicated that PROs provide distinct prognostic information beyond standard clinical measures in cancer clinical trials.

Conclusion
PROs might be considered for stratification purposes in future trials, as they were often better predictors of survival than PS. Studies are needed to determine whether interventions that improve PROs also increase survival and to identify explanatory mechanisms through which PROs relate to survival.

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INTRODUCTION

Patient perspectives are increasingly used as outcomes in cancer clinical trials, as well as in cancer surveillance and patient care.[1] The United States Food and Drug Administration has recently drawn additional attention to these variables by defining patient-reported outcomes (PROs) as "measurement of any aspect of a patient's health status that comes directly from the patient (ie, without the interpretation of the patient's responses by a physician or anyone else)," including disease symptoms, patient functioning, and quality of life (QOL).[2]

PROs provide an assessment of patient well-being, but do they have other uses, such as predicting how long patients will survive? The predictive value of PROs, particularly QOL, for cancer survival has been noted in descriptive reviews.[3-5] However, no systematic overviews have assessed the robustness of this observation and investigated whether PROs provide prognostic information that goes beyond standard biomedical predictors.

This article provides a comprehensive critical review of cancer clinical trials that examined the relationship between PROs, biomedical predictors, and survival. The rationale for focusing this review on clinical trials was to control for effects of treatment: in other words, trials ensure that all patients are treated using a specified protocol, thus ensuring that baseline PROs (and other potential confounders, such as comorbidity) do not affect treatment and its effects on survival. Specifically, we wanted to determine the following: the relationship between PRO end points and cancer patient survival, the effect size of relationships reported, and implications for future research and clinical practice.

SEARCH STRATEGY AND SELECTION CRITERIA

MEDLINE searches were conducted for English-language studies in cancer patients using the terms "quality of life" or "patient-reported outcome," "cancer," and "prognostic" or "survival." Searches were also conducted using words denoting specific PRO domains and scale acronyms often associated with PRO reporting. The following search terms were also used: depression, anxiety, fatigue, baseline pain, CES-D, BDI, QLQ-C30, STAI, RSCL, PAIS, HADS, BPI, MSAS, pain assessment, functional assessment, FACT questionnaire, FACT survey, FLIC, self-rated health. These searches were supplemented by reference list searches, the Cochrane database, American Society of Clinical Oncology and European Society for Medical Oncology abstracts, hand searches, and expert consultation.

Studies that met the following criteria were selected:

1. Include at least one PRO, defined as patient-reported indicator of well-being, including single (eg, pain) and multidimensional outcomes (eg, QOL). Studies that used only proxy ratings from health providers or others or measures of nonoutcome psychological constructs (eg, coping styles) were excluded.

2. Include data on survival/mortality.

3. Based on a prospective phase II, III, or IV clinical trial of cancer treatment. No phase IV trials were identified.

4. Include at least one multivariate analysis examining PROs and survival. A multivariate analysis was defined as any statistical test to examine the effects of one or more PRO on survival and that controlled for one or more clinical, disease-related factors.

5. Include baseline PRO data in analyses. Studies that reported only changes in PROs were excluded because such measures may reflect rather than predict changes in survival time related to disease status.

RESULTS

A total of 39 published articles (1989 through 2006) met all inclusion criteria. Data were abstracted and independently reviewed by at least two raters. Summaries of key data can be seen in Tables 1 and 2[6-44]; the majority of studies were in populations with primarily advanced or metastatic disease (Table 1). Several studies included multiple stages of disease in the same article or focused on nonmetastatic disease, but even many of these reports included large numbers of patients with advanced disease (Table 2). Study characteristics and findings were consistent across metastatic and nonmetastatic disease populations, and combined results are presented here. Studies on lung (n = 12) and breast cancer (n = 8) were most prevalent. Overall, 13,874 cancer patients provided PRO ratings, with a mean of 356 patients per study (range, 40 to 2,270 patients). Most studies (n = 29) were phase III trials.

PRO Assessment

QOL was the most common PRO assessed. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) or its modules were used in 56% of studies. Other measures included QOL questionnaires (eg, the Functional Living Index–Cancer and general and site-specific versions of the Functional Assessment of Cancer Treatment [FACT]) and measures of specific dimensions such as pain. Some studies assessed numerous PROs,[7,37] such as Brown et al, [7] who used five linear analog scales of well-being: the FACT-Brain, the Symptom Distress Scale, and the Profile of Mood States short-form. See references[1,45] for information on specific questionnaires.

Biomedical Variable Assessment

Most studies included multiple clinical parameters. These included treatment arm, stage (tumor size, nodal status, extent and site of metastases), weight loss, and serum markers (eg, albumin, hemoglobin), among others. Most studies (n = 37) included a clinician-rated assessment of performance status (PS). In many cases, a minimum PS score was used for eligibility.

Analytic Methods

Approaches varied considerably. Most commonly, initial univariate analyses examined individual relationships between possible prognostic factors (PROs, biologic, and clinical factors). Subsequent multivariate analyses examined combined effects of PRO, disease, and clinical variables. The analytic strategy used in most articles (n = 35) was the Cox proportional hazards model. This approach is well-suited to assess the effect of multiple independent variables (PROs, disease variables) on an outcome (survival) over time. In several cases, other approaches were used because of violation of assumptions needed for a Cox analysis.[10,11,37,39] The way that independent variables were selected for entry into the regression varied, including selection of predictors based on the univariate analyses or other methods, forward and backward selection (using significance levels for inclusion varying from .05 to .15), and bootstrap methodology.[7] A common approach was to include the selected clinical and sociodemographic variables first and then explore whether PROs provided additional explanatory value in predicting survival.

Follow-Up

Follow-up times varied from study to study, especially across cancer sites. Not all periods of follow-up could be determined from the articles, but they ranged from 12 weeks in the lung study by Brown et al[6] to nearly 10 years, as in the study on esophagogastric cancer by Chau et al.[8]

Findings

In 36 studies, at least one PRO was significantly associated with survival in the multivariate analysis. Global QOL and physical functioning each predicted survival more often than other PROs, with significant findings in 15 and 11 studies, respectively, though rarely simultaneously significant in the same study.[8,29,38] Certain symptom measures frequently predicted survival: appetite/appetite loss (n = 10), fatigue (n = 6), and pain (n = 7), as well as mood/emotion functioning (n = 5) and role functioning (n = 6).

All three articles in which no PROs were significantly associated with survival in the multivariate analysis were in breast cancer.[12,18,40] Coates et al[12] presented further follow-up analyses of the subset of women who experienced recurrence and found that PROs collected near the time of recurrence were significant predictors of survival.

Most associations between PROs and survival were in the expected direction, ie, better PROs predicted better survival, with a few

Table 1. Study Characteristics, Measures, and Results: Primarily Metastatic Cancer

Cancer Type	First Author and Year	Patients/N*	PRO Assessments†	PROs Related to Survival	Hazard Ratio	CI
Bladder	Roychowdhury (2003)[35]	N = 364 Metastatic: n = 236 Locally advanced (T4b, N2, N3): n = 128	EORTC QLQ-C30‡	Physical function Role function Appetite loss	0.64 1.41 1.84	0.48 to 0.87§ 1.03 to 1.96§ 1.36 to 2.49‖
Brain	Brown (2005)[7]	N = 194 T3: n = 26 T4: n = 168	5 LASAs FACT-Brain SDS Epworth Sleepiness Scale Profile of Mood States-Short Form	Fatigue	0.99	0.98 to 1.00
	Meyers (2000)[30]	N = 80 Recurrent: n = 80 Glioblastoma multiforme: n = 54 Anaplastic glioma: n = 26	FACT-Brain Functional Independence Measure 7 cognitive batteries	Digit span (battery)¶ Digit symbol (battery)¶ HVLT recog (battery)¶	1.245 0.852 0.831	1.109 to 1.397# 0.749 to 0.970# 0.762 to 0.906#
Breast	Coates (1992)[10]	N = 226 metastatic	6 LASAs	Physical function without QLI Physical function with QLI	0.988 0.989	0.978 to 0.998# 0.979 to 0.999#
	Efficace (2004)[16]	N = 219 metastatic	EORTC QLQ-C30	Appetite loss	1.008	1.002 to 1.013‖
	Kramer (2000)[25]	N = 187 metastatic	EORTC QLQ-C30‡	Pain	NR	NR*
	Seidman (1995)[37]	N = 49 metastatic	FLIC Memorial Symptom Assessment Scale (MSAS) MSAS-Global Distress Index (MSAS-GDI) RAND Mental Health Inventory pain questionnaire Memorial Pain Assessment Card	Global QOL MSAS-GDI	NR NR	NR NR
	Winer (2004)[41]	N = 451 metastatic	FLIC SDS	Global QOL SDS	NR NR	NR NR
Cervical	Monk (2005)[32]	N = 284 Stage IVB	FACT-Cervical (Cx) FACT/GOG-Ntx subscale Brief Pain Inventory UNISCALE	FACT-Cx	0.91	0.86 to 0.97**
Colorectal	Efficace (2006)[17]	N = 299 metstatic	EORTC QLQ-C30	Social function	0.991	0.987 to 0.996
	Maisey (2002)[29]	N = 501 locally advanced: 90 metastatic: 411	EORTC QLQ-C30‡	Physical function Role function Social function Emotional function Nausea Pain Dyspnea Sleep disturbance Global QOL	0.74 0.75 0.70 0.78 1.56 1.69 1.43 1.49 0.46	0.59 to 0.93§ 0.60 to 0.93§ 0.55 to 0.88§ 0.64 to 0.96§ 1.19 to 2.04§‖ 1.35 to 2.08§‖ 1.14 to 1.79§‖ 1.18 to 1.89§‖ 0.37 to 0.57§
Lung	Efficace (2006)[43]	N = 391 Stage IIIB/IV	EORTC QLQ-C30 QLQ-LC13	Pain Dysphagia	1.11 1.12	1.07 to 1.16**‖ 1.04 to 1.21**‖
	Eton (2003)[19]	N = 573 Stage IIIB: 108 Stage IV: 465	FACT-Lung v2	Physical function	0.95	0.94 to 0.97
	Ganz (1991)[21]	N = 40 metastatic	FLIC	Global QOL	0.969	0.946 to 0.992#
	Herndon (1999)[22]	N = 206 metastatic	EORTC QLQ-C30 Duke-UNC Social Support Scale	Pain	1.006	NR‖
	Maione (2005)[28]	N = 566 Stage IIIB: 178 Stage IV: 388	EORTC QLQ-C30 global QOL‡ Activities of Daily Living (ADL)‡ Instrumental ADL (IADL)‡	IADL Intermediate functioning Worse functioning Global QOL Intermediate QOL Worse QOL	 0.97 1.31 1.62 1.76	 0.76 to 1.22 1.00 to 1.71 1.24 to 2.10 1.29 to 2.39

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Table 1. Study Characteristics, Measures, and Results: Primarily Metastatic Cancer (continued)

Cancer Type	First Author and Year	Patients/N*	PRO Assessments†	PROs Related to Survival	Hazard Ratio	CI
	Moinpour (2002)[31]	N = 222 Stage IIIB/IV	FACT-L‡	Global QOL	NR	NR
Melanoma	Chiarion-Sileni (2003)[9]	N = 140 metestatic	Rotterdam Symptom Check List‡	Global QOL Physical symptom distress	0.43 1.92	0.20 to 0.92§ 1.10 to 3.36‖
	Coates (1993)[11]	N = 152	LASAs	Appetite Global QOL	0.818 0.851	0.710 to 0.942# 0.738 to 0.982#
		metastatic		Mood	NR	NR
Multiple myeloma	Dubois (2006)[15]	N = 144 refractory	EORTC QLQ-C30 QLQ-MY24 FACIT-Fatigue scale FACT/GOG-Ntx subscale	Fatigue (from FACIT)	0.952	NR
	Wisloff (1997)[42]	N = 468	EORTC QLQ-C30‡	Physical function Lower functioning Intermediate functioning Cognitive function Lower cognition Intermediate cognition	 1.67 1.05 1.58 1.17	 1.05 to 2.68 0.67 to 1.64 1.02 to 2.44 0.82 to 1.67
			Skeletal disease ranged from normal to limited to extensive			
Prostate	Collette (2004)[13]	N = 391 metastatic HRPC	EORTC QLQ-C30	Insomnia Appetite loss	1.45 1.47	1.15 to 1.84‖ 1.16 to 1.86‖
	Fossa (1992)[20]	N = 58 metastatic HRPC	Own scales (Likert)‡	Fatigue	NR	NR
	Sullivan (2006)[38]	N = 809 Bone metastasis: n = 690 (only bone metastasis: n = 476) Only soft tissue mets: n = 97 No mets: n = 22	EORTC QLQ-C30‡ FACT-G/FACT-P‡	Global QOL (FACT-P) FACT-P composite Global QOL (FACT-G) Physical function (FACT-G) Role function Physical function Pain Global QOL Fatigue Constipation Social function Pain symptoms (FACT-P PCS) Functional wb (FACT-G) Appetite loss	0.73 0.67 0.76 0.69 0.68 0.75 1.25 0.69 1.39 1.36 0.81 0.60 0.73 1.61	0.59 to 0.90 0.54 to 0.83 0.62 to 0.93 0.56 to 0.86 0.55 to 0.84 0.60 to 0.93 1.01 to 1.54‖ 0.56 to 0.85 1.13 to 1.70‖ 1.10 to 1.69‖ 0.66 to 1.00 0.49 to 0.75 0.59 to 0.89 1.28 to 2.02‖
	Tannock (1996)[39]	N = 161 Metastatic HRPC	EORTC QLQ-C30 Prostate-specific EORTC-based scale Prostate Cancer-Specific QOL Instrument	Appetite loss Present pain intensity Pain Physical function	NR	NR
Mixed	Loprinzi (1994)[27]	N = 1,077 Advanced Colorectal: n = 515 SCLC: n = 357 NSCLC: n = 205	Own questionnaire, including patient-judged ECOG PS and patient-judged KPS	Patient-judged KPS Appetite	NR NR	NR NR

Abbreviations: PRO, patient-reported outcome; CES-D, Center for Epidemiologic Studies Depression scale; FACIT, Functional Assessment of Chronic Illness; FACT/FACT-G, Functional Assessment of Cancer Therapy; FACT-L, Functional Assessment of Cancer Therapy, lung module; FACT-P, Functional Assessment of Cancer Therapy, prostate module; FLIC, Functional Living Index-Cancer; LASA, Linear Analog Self-Assessment; MSAS, Memorial Symptom Assessment Scale; QLI, Quality of Life Index; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-LC17, Quality of Life Questionnaire lung cancer module; SDS, Symptom Distress Scale; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; KPS, Karnofsky Performance Status; MOS, Medical Outcomes Study; UNC, University of North Carolina.

*N refers to the number of study participants who completed PRO assessments, NR means not reported.

†References and discussion of most of the PRO assessments used can be found in Spilker.[45] A full list of PRO questionnaires and references is available from the authors on request.

‡Unless noted with a double dagger (‡), the independent variables were measured on a continuous scale (thus usually providing smaller hazard ratios).

§Hazard ratios and confidence intervals were inverted to provide for consistency in cases where higher values indicated worse functioning.

‖For these symptom measures, higher scores indicated greater levels symptom distress.

#Hazard ratios were computed based on coefficient values provided in the manuscript (hazard ratio = exponential of the regression coefficient).

**Hazard ratios are based on 10-point increases in scale scoring.

Table 2. Study Characteristics, Measures, and Results: Other Cancer

Cancer Type	First Author and Year	Patients/N*	PRO Assessments†	PROs Related to Survival	Hazard Ratio	95% CI
Breast	Coates (2000)[12]	Substudy 1: adjuvant N = 2270	3 LASAs	None	n/a	
		Substudy 2: PRO assessed at 1 month postrelapse	3 LASAs			
		Premenopausal: n = 203		Premenopausal: mood	0.92	NR*
		Postmenopausal: n = 149		Postmenopausal: appetite	0.88	NR
		Substudy 3: PRO assessed at 6 months postrelapse	3 LASAs	Premenopausal: physical function	0.91	NR
		Premenopausal: n = 219		Premenopausal: appetite	0.92	NR
		Postmenopausal: n = 162		Postmenopausal: physical function	0.85	NR
				Postmenopausal: mood	0.88	NR
				Postmenopausal: appetite	0.86	NR
	Efficace (2004)[18]	N = 359	EORTC QLQ-C30	None	n/a	
		Inflammatory: n = 173				
		Locally advanced: n = 186				
	Tross (1996)[40]	N = 280 stage II	Global Severity Index/ Symptom Check List 90-Revised‡	None	n/a	
Esophagogastric	Chau (2004)[8]	N = 817, most metastatic; 20% locally advanced	EORTC QLQ-C30‡	Physical function	0.760	0.597 to 0.968
				Role function	0.690	0.543 to 0.877
				Global QOL	0.572	0.452 to 0.724
Liver	Yeo (2006)[44]	N = 233, unresectable or metastatic, 12% stage I/II	EORTC QLQ-C30	Appetite loss	1.070	1.023 to 1.118#‖
				Physical function	0.911	0.856 to 0.969#
				Role function	0.944	0.894 to 0.996#
Lung	Brown (2005)[6]	N = 239, all stages, mostly III/IV	EORTC QLQ-C30; QLQ-LC17	Global QOL	0.98	NR
				Role function	0.99	NR
				Fatigue	0.98	NR
				Appetite loss	1.01	NR
				Constipation	1.02	NR
	Kaasa (1989)[24]	N = 102	Author's psychosocial well-being index‡	General symptoms	0.554	0.360 to 0.853¶
		Stage II: n = 14	Independent items‡	Psychosocial well-being	0.638	0.414 to 0.981¶
		Stage III: n = 88		Physical function	NR	
	Langendijk (2000)[26]	N = 198	EORTC QLQ-C30	Global QOL	0.9784	0.9687 to 0.9882
		Stage I: n = 53				
		Stage II: n = 2				
		Stage IIIA: n = 65				
		Stage IIIB: n = 78				
	Naughton (2002)[33]	N = 67	EORTC QLQ-C30	Symptoms	1.039	NR‖
			Sleep quality scale	Depression (both borderline significant)	2.442	NR
		SCLC	CES-D short form‡			
			MOS Social Support Questionnaire			
	Nowak (2004)[34]	N = 53	EORTC QLQ-C30‡	Fatigue	NR	
		Mesothelioma: n = 53	QLQ-LC13‡	Pain	NR	
		Stage I: n = 6				
		Stage II: n = 0				
		Stage III: n = 33				
		Stage IV: n = 13				
		Unable to stage: n = 1				
	Ruckdeschel (1994)[36]	N = 438	fLIC	Global QOL	0.98	0.97 to 0.98
		NSCLC: n = 330				
		SCLC: n = 26				
		Mesothelioma: n = 48				
		Malignant effusions: n = 34				
Lymphoma	Jerkeman (2001)[23]	N = 92 all stages; aggressive disease with favorable prognosis	EORTC QLQ-C30‡	Global QOL	0.127	0.019 to 0.833§

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Table 2. Study Characteristics, Measures, and Results: Other Cancer (continued)

Cancer Type	First Author and Year	Patients/N*	PRO Assessments†	PROs Related to Survival	Hazard Ratio	95% CI
Mixed	Dancy (1997)[14]	N = 474 Stage I/II: n = 157 Stage III/IV: n = 315 Lung: n = 179 Ovary: n = 133 Breast: n = 83 Head and neck: n = 11 Lymphoma: n = 8 Other: n = 60	EORTC QLQ-C30‡	Global QOL Emotional function	0.56 1.71	NR NR

Abbreviations: PRO, patient-reported outcome; CES-D, Center for Epidemiologic Studies Depression scale; FACIT, Functional Assessment of Chronic Illness; FACT/FACT-G, Functional Assessment of Cancer Therapy; FACT-L, Functional Assessment of Cancer Therapy, lung module; FACT-P, Functional Assessment of Cancer Therapy, prostate module; FLIC, Functional Living Index-Cancer; LASA, Linear Analog Self-Assessment; MSAS, Memorial Symptom Assessment Scale; QLI, Quality of Life Index; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-LC17, Quality of Life Questionnaire lung cancer module; SDS, Symptom Distress Scale; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; KPS, Karnofsky Performance Status; MOS, Medical Outcomes Study; UNC, University of North Carolina.

*N refers to the number of study participants who completed PRO assessments, NR means not reported.

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‡Unless noted with a double dagger (‡), the independent variables were measured on a continuous scale thus usually providing smaller hazard ratios.

#Hazard ratios are based on 10-point increases in scale scoring.

‖For these symptom measures, higher scores indicated greater levels symptom distress.

¶Hazard ratios were computed based on coefficient values provided in the manuscript (hazard ratio = exponential of the regression coefficient).

§Hazard ratios and confidence intervals were inverted to provide for consistency in cases where higher values indicated worse functioning.

exceptions: better emotional functioning,[14] reduced fatigue,[6] and better role functioning[35] were associated with an increased risk of death.

Effect Size

The size of the PRO effect was reported inconsistently and in some cases, not at all, with only statistical significance reported. Many investigators reported hazard ratios. In a few studies, hazard ratios were calculated such that greater risk was attributed to lower QOL scores, whereas in most studies, hazard ratios were computed for increasing scores, with lower risk being associated with better QOL. In Tables 1 and 2, we inverted hazard ratios and CIs as needed to provide consistent interpretation across all studies. Although most investigators treated PRO parameters as continuous variables (usually providing hazard ratios closer to 1), some used dichotomized variables based on median values, as indicated by asterisks in Tables 1 and 2. It should be noted that for measures of symptoms, higher scores reflect higher levels of symptoms and hence lower well-being, whereas the opposite is true for positively valenced constructs (eg, global QOL).

We characterized relative effect sizes for hazard ratios as moderate (either protective [.51 to 0.75] or contributory [1.35 to 1.99]) and large (less than 0.50 or in excess of 2), based on ratings used by the Institute of Medicine.[46] It can be seen that, although statistically significant, the size of many reported effects was small. However, a number of articles reported moderate[8,13,14,24,28,35,38,42] or large effects.[9,23,29,33] The finding of Jerkeman et al[23] that global QOL ratings were associated with nearly an eight-fold difference in survival rates was particularly striking.

DISCUSSION

This article reviewed data relating PROs measured at baseline to cancer patient survival, based on an analysis of published clinical trials. The use of clinical trials provides several advantages: well-characterized samples, use of consistent treatment protocols not based on PRO ratings, few patient comorbid conditions (owing to eligibility criteria), availability of mature data for adequately powered analyses, and rigorous quality control. In general, the quality of trials included here was high. At the same time, using clinical trials presents limitations: there were few trials in early-stage disease[47] and trial participants were unrepresentative of the broader cancer patient population.[48] In addition, we did not include unpublished analyses nor articles not published in English.

The studies reflect considerable diversity—in patients, measures of PROs and correlates, and analytic strategies, complicating cross-study comparisons. Statistical models, particularly related to selection of PROs assessed and entered into analysis, were not theory-based. Although we do not have access to the original study protocols, analyses were described as ad hoc and exploratory, making it unlikely that examining relationships between PROs and survival was specified as an a priori primary or secondary hypothesis. PRO measures included single items and symptoms, multi-item batteries, broad constructs, and specific aspects of well-being. In most studies, relationships among closely related measures were not explored, nor were attempts made at item reduction, with the implication that considerable overlap, or multicollinearity, was likely across items; Efficace et al[16] cited this factor as a possible explanation for why the PRO with the narrowest interpretation (appetite loss) emerged as the strongest factor in analysis, because the other PROs, in effect, may have canceled each other out. There were often multiple factors entered into analyses, with little attention to adjusting Type I error rates for multiple comparisons; consequently, it is likely that some findings are spurious and owing to chance. Not all articles included adequate information regarding follow-up time, and even some that did neglected to provide any reasoning behind the selection of those time periods. In addition, the clinical significance of PRO scores and effect sizes was rarely discussed. Dubois et al[15] is an exemplary exception, with clinical

significance of scores and effect sizes being specified a priori, building on contemporary advances in defining clinical significance.[49]

Although the studies here can be seen as forming a solid base for hypothesis generation, the next generation of research in this area should include focused hypotheses and measures. For example, specific measures that are believed to predict survival should be specified a priori, as opposed to using a broad range of nonspecific assessments, which often gives rise to inconsistent or conflicting findings. In addition, studies that go beyond documenting the phenomenon and test hypotheses about why PROs may be linked to survival are strongly indicated.

Despite this heterogeneity, there is impressive agreement across studies supporting the link between PROs and survival. But what about the three studies that found no PROs predicted survival in multivariate analysis? It is noteworthy that all three were conducted with nonmetastatic breast cancer patients. In early-stage breast cancer, extended survival for many years is expected. It seems plausible that PROs assessed years before death may not predict survival length, as many subsequent events (eg, diagnosis of comorbidities) are more likely to affect life span. This hypothesis was supported by the study by Wisloff et al[42] of multiple myeloma patients, where the relationship between baseline QOL and survival was strongest in the first 1 to 2 years of follow-up.

In addition, for two of the three studies which found paradoxical relationships between PROs and survival, the authors further elaborated on their findings by adding interaction terms: Dancey et al[14] found that emotional functioning was not associated with survival in patients with high global QOL, and that only in those with low global QOL did higher emotional functioning predict an increased risk of death. Roychowdhury et al[35] reported that whereas their initial findings indicated that high role functioning was associated with a greater mortality risk, this depended on metastatic status; in patients without visceral metastasis, those with increased role functioning lived longer. The relationships between PROs and survival may be more complicated than main effects and again require causal models that are subjected to empirical testing.

For studies that found a PRO-survival relationship, PROs retained predictive power after considerable variance in survival outcomes had been explained by well-established and powerful biomedical predictors, such as stage. Even given that there was a limited amount of variance to be explained, PROs were predictive, and many effect sizes were impressive. Even more remarkable, PROs generally remained significant predictors of survival even after accounting for PS ratings. In fact, in a number of studies, PS no longer held explanatory value once PROs had been entered into the analysis.[9-11,15-17,20-26,29,30,33-35,40,43,44] PS is based on patient behaviors and functional ability, rather than disease characteristics, and is similar to some PROs (eg, ratings of physical and role functioning). Likewise, some toxicity indicators were linked to survival, but not as strongly as the associated patient symptom ratings. Both PS and toxicity ratings are based on clinician perspectives, rather than those of patients, and it seems that patient ratings are more sensitive in predicting how long they will live.

Why should PROs be so consistently linked with survival? There are several possible explanations.

1. PROs better reflect survival-related patient functioning and well-being than traditional prognostic indicators. This may be because PROs ask different questions and reflect distinct aspects of well-being, PROs use more sensitive scales of response than relatively crude PS and toxicity measures, and patients have a different perspective regarding their functioning that is more closely related to survival. There is support for all of these points. PRO measures include many items not typically included as part of standard clinical records (eg, assessment of certain symptoms and domains), with multiple response options. Considerable research has also demonstrated the lack of concordance between proxy and patient PRO ratings.[50] Maisey et al[29] postulate that PROs may reflect biologic parameters not picked up by other prognostic indicators.

2. PROs pick up prognostically relevant lowered patient well-being earlier than other measures. There is support for this hypothesis. Morton et al[51] found that PRO ratings in colorectal cancer patients experiencing peripheral neuropathy ($n = 696$) detected worsening of their symptoms 2 to 3 months earlier than did Common Toxicity Criteria ratings.

3. Higher PRO scores are linked with more positive behaviors, such as adherence to medical regimens and healthy lifestyles, that affect survival. Little directly relevant information is available to address this hypothesis. However, Courneya et al[52] found that QOL was a significant correlate of adherence to an exercise training program in prostate cancer survivors. The relationship between PROs and health behaviors deserves additional study.

4. PRO scores reflect individual characteristics that affect the disease process; in other words, patient self assessments have biologic significance that can affect tumor behavior and survival. There is extensive but conflicting literature on the relationship between psychosocial variables (eg, personality, coping styles) and cancer incidence and survival.[53] Kemeny[54] suggests that a systematic and coordinated research program is needed that tests the relationship between psychological factors (eg, PROs), behaviors, biologic mediators (eg, immunologic factors, DNA repair mechanisms, tumor suppressor genes, apoptosis regulators), and biologic outcomes. Until research of this nature has been reported, the notion that PROs directly affect cancer outcomes remains speculative.

What are the implications of these findings?

1. PROs provide distinct prognostic information beyond standard clinical measures. The articles described here provide ample support for this contention and support their use to facilitate patient-clinician discussion. Some articles outside the scope of this review also investigated the prognostic importance of changes in PROs and found, not surprisingly, that patients who reported worsening PROs were apt to also have worsening disease outcomes.[38] Because PROs may deteriorate before disease progression is evident by other measures, changes in serial PROs may provide an early warning system that can be useful for clinical decision making.

2. PROs might be considered for stratification in clinical trials, as they are better predictors of survival than other variables such as PS. This suggestion, which was first offered by Osoba,[4,55] could ensure that treatment groups are comparable on important PRO dimensions, thus enhancing conclusions about treatment efficacy. However, despite the promise of PROs to provide more sensitive stratification criteria, more work is needed to determine appropriate cut points, the most appropriate PRO measures and scales, and how PROs could provide a basis for eligibility determination. Technologic advances (ie, widespread use of touch-screen computers) could facilitate the PRO assessment and use for such purposes, as well as enhance the interpretation of such ratings.[49]

3. Interventions that improve PROs have the potential to increase survival. This implication is intriguing and largely untested in advanced disease populations like most of those in these studies. A few notable exceptions (eg, two studies that investigated the effects of group interventions in advanced breast cancer on survival[56,57]) came to opposite conclusions. To begin to elucidate this issue, future such investigations need to assess specified PRO domains and mediating biologic and behavioral processes. In addition, approaches that target multiple dimensions of patient well-being, such as a recent multicomponent intervention reported by Rummans et al,[58] may be more effective in improving well-being than narrowly focused psychosocial programs. Interventions that improve PROs also have merit in reducing suffering from cancer, even if they do not increase survival time.

4. The role of PROs in health care needs to be considered more broadly. The predictive value of PROs extends to populations other than cancer patients. For example, patient QOL ratings predict mortality in patients with arthritis,[59] obstructive lung diseases,[60] HIV,[61] and dialysis,[62] as well as in patients seen at ambulatory primary care clinics[63] and community-based health care for senior citizens.[64] Understanding why patients' own perspectives on well-being affect their longevity, as well as how to use this information in health care, holds tremendous promise in improving health outcomes.

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