REVIEW

Health-Related Quality-of-Life Measurement in Randomized Clinical Trials in Breast Cancer—Taking Stock

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Measurement of health-related quality-of-life (HRQOL) in randomized clinical trials in breast cancer has become common. In this review, we take stock of the contribution that HRQOL measurement in breast cancer clinical trials makes to clinical decision making regarding selection of optimal treatment. A series of MEDLINE searches was conducted to identify all randomized trials in breast cancer that included self-reported HRQOL or psychosocial outcomes. A total of 256 citations were identified that included HRQOL or psychosocial outcomes in breast cancer patients, and 66 of these involved randomized clinical trials of treatment. These 66 reports of breast cancer clinical trials of treatment are discussed in this review. Forty-six of the trials evaluated biomedical interventions, and 20 evaluated psychosocial interventions. Among the biomedical trials, eight trials evaluated HRQOL in primary management of breast cancer, seven trials evaluated HRQOL in adjuvant therapy of breast cancer patients, 20 trials involved metastatic breast cancer, eight trials involved symptom control/supportive care, and three trials evaluated different approaches to investigation or follow-up of breast cancer patients. Among the psychosocial trials, 13 trials evaluated HRQOL in adjuvant therapy of breast cancer patients, and their partners or spouses, six trials involved metastatic breast cancer, and one trial focused on symptom control. We found that the contribution of HRQOL measurement to clinical decision making depended on the clinical setting. In primary management of breast cancer, where medical outcomes of several treatment options are equivalent, HRQOL measurement provided added information for clinical decision making beyond that of traditional medical outcomes. In trials in the adjuvant setting, HRQOL measurement did not influence clinical decision making. In metastatic disease, HRQOL outcomes provided little information beyond that obtained from traditional medical outcomes, including toxicity. In the symptom control/supportive care setting, results of HRQOL questionnaires targeting specific symptoms (e.g., emesis) guided treatment decisions. In psychosocial intervention trials, psychosocial and/or HRQOL measurements often provided the only outcome information; therefore, selection of instruments that captured attributes likely to be altered by the intervention was essential. Until results of ongoing trials in breast cancer are available, caution is recommended in initiating new HRQOL studies unless treatment equivalency is expected, or unless the HRQOL questions target unique or specific issues that can only be addressed through patient self-report, including outcomes of psychosocial interventions. [J Natl Cancer Inst 2003;95:263–81]

Measurement of health-related quality-of-life (HRQOL) in patients with breast cancer, and in cancer patients in general, has been a major research focus over the past quarter century. This interest in HRQOL is reflected in the development and validation of HRQOL instruments by groups in both North America *(1)* and Europe *(2)*, and by the almost routine inclusion of HRQOL measurement in clinical trials of breast cancer patients. The HRQOL data are intended to help guide clinical decision making regarding selection of optimal treatment, to provide information about the experience of patients receiving treatment and, potentially, to predict prognosis. The first of these goals is best addressed in the context of randomized clinical trials, whereas the latter two goals can often be addressed by using a variety of observational and interventional study designs.

Measurement of HRQOL in randomized clinical trials increases burden on study participants, enhances trial complexity, and is time-consuming and expensive. Although there is a general consensus that HRQOL measurements increase the comprehensiveness of clinical trial outcomes and enhance understanding of treatment effects, the extent to which currently available HRQOL instruments provide information beyond that obtained with other outcome measures (e.g., tumor recurrence or response, survival, toxicity, and performance status) is not clear. Nor is it clear whether HRQOL measurements influence clinical decision making or whether the contribution of HRQOL measurement to clinical decision making varies according to stage of disease or type of intervention (i.e., biomedical or psychosocial).

The latter distinction is particularly important to planners of clinical trials—that is, if HRQOL measurement is of greater value in patients with particular stages of disease than in others, or in some clinical settings than in others, then efforts (and resources) can be shifted to those settings. In this review, we examine the contribution of HRQOL measurement to treatment selection in a variety of clinical settings, and we attempt to identify those settings in which HRQOL measurement is likely

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See "Notes" following "References."

Journal of the National Cancer Institute, Vol. 95, No. 4,

to have the greatest impact on selection of optimal treatments. Potential factors contributing to this assessment include equivalency (or nonequivalency) of the treatments being compared, the goals of treatment (prolongation of survival versus palliation), the severity of disease symptoms and treatment toxicity, and the outcomes (i.e., medical versus psychosocial) that are likely to be influenced by the treatment(s) being studied.

This review arises out of activities of the Cancer Outcomes Measurement Working Group of the National Cancer Institute (NCI), which is examining a broad range of HRQOL research in a spectrum of commonly occurring cancers. Many of the group's activities will be reported elsewhere. Here we focus on a specific issue—the contribution of HRQOL measurements in breast cancer clinical trials to the selection of optimal treatment in various clinical settings. Specifically, in this review, we take stock of what has already been learned from HRQOL measurement in clinical trials in breast cancer patients, focusing on the impact of these measurements on clinical decision making regarding selection of optimal treatments over and above the impact of more traditional medical outcomes (e.g., response, survival, and toxicity). We define HRQOL measurement as the self-report of the impact of breast cancer and its treatment on some aspect of function (e.g., physical, role, emotional, or social). Consequently, measurement of self-reported symptoms only (e.g., pain and nausea) or recording of toxicity only was not considered an HRQOL measurement. The decision to exclude studies that recorded self-reported symptoms and/or toxicity only was made to facilitate identification of the impact of the more recently developed HRQOL measurement approaches on treatment selection. It was not intended to minimize the importance of the measurement of symptoms and/or toxicity in breast cancer patients. Nor was our focus on the contribution of HRQOL measurement to treatment selection intended to undermine the importance of HRQOL measurement in describing the experience of cancer patients or in predicting prognosis.

Purpose of the Review

Our objectives were to 1) assemble the literature on HRQOL measurement in randomized clinical trials in breast cancer, including all HRQOL instruments meeting the above definition; 2) identify the most frequently used HRQOL measurement instruments; 3) describe HRQOL measurement in breast cancer clinical trials with respect to time trends (Table 1), phase of disease and its treatment, and types of intervention studied; 4) determine the incremental contribution of HRQOL measurement to clinical decision making beyond that of traditional medical outcomes (including toxicity); and 5) identify areas for future research involving HRQOL measurement in clinical trials in breast cancer.

Search Methods

A series of computerized MEDLINE database searches were conducted in May and June of 2001 using the following unrestricted search strategies: breast cancer and [1] QOL, [2] QOL and instruments, [3] Hospital Anxiety and Depression Scale (HADS), [4] Cancer Rehabilitation Scale (CARES), [5] Functional Living Index for Cancer (FLIC), [6] European Organisation for Research and Treatment of Cancer QOL Questionnaire C-30 (EORTC QLQ-C30), [7] Functional Assessment of Cancer Therapy (FACT), [8] Breast Cancer Chemotherapy Questionnaire (BCQ), [9] Profile of Mood States (POMS), [10] Medical Outcomes Study Short Form 36 (MOS-SF-36), [11] Symptom Distress Scale (SDS), [12] Rotterdam Symptom Checklist (RSCL), [13] State Trait Anxiety Index (STAI), [14] QOL and randomized trials, and [15] QOL and clinical trials. These searches were supplemented by more focused MEDLINE searches to identify companion publications (e.g., follow-up articles and reporting of medical outcomes) and to further explore areas in which few articles were identified (e.g., adjuvant therapy). MEDLINE searches were supplemented by reviews of authors' files and discussions with leading experts to identify additional trials that had not been identified in the computerized literature searches described above. For the purposes of this review, we used articles meeting the following criteria: 1) full reports published in English after 1975; 2) randomized clinical trials of breast cancer treatment (not prevention), including surgery, chemotherapy, hormone therapy, supportive care, or psy-

Table 1. Distribution of randomized clinical trials for breast cancer treatment by publication year, type of intervention (i.e., biomedical and psychosocial), and phase of illness and its treatment*

	1980–1984	1985–1989	1990–1994	1995–1999	2000–2001†	Total
Biomedical intervention						
Primary management	0	3	2	2	1	8
Adjuvant setting	0	0	0	5	2	7
Metastatic disease	0	2	3	9	6	20
Follow-up	0	0	2	1	0	3
Symptom control	0	0	5	2	1	8
Subtotal	0	5	12	19	10	46
Psychosocial intervention‡						
Adjuvant setting	1	1	0	6	5	13
Metastatic disease	1	0	1	2	2	6
Symptom control	0	0	0	0	1	1
Subtotal	2	1	1	8	8	20
Total	2	6	13	27	18	66

*Trials were identified among articles published from 1975 through 2001. There were no randomized clinical trials that included HRQOL measures identified from 1975 through 1979. Trials of treatment of the primary breast tumor are included under "Primary management," trials of interventions administered after local therapy (and in the absence of systemic metastases) are included under "Adjuvant setting," trials in women with known metastases are included under "Metastatic disease," trials in well women not receiving active treatment are included under "Follow-up," and trials of interventions targeting specific symptoms are included under "Symptom control."

†January 1, 2000, through June 30, 2001.

‡There were no psychosocial intervention trials focused exclusively on the "primary management" or "follow-up" settings.

chosocial intervention; 3) documentation of HRQOL outcomes (trials that measured utilities only were excluded because of the single-item nature of utility measurement); 4) use of a patient self-report measure that examined general HRQOL, cancer-specific or breast cancer-specific HRQOL, or psychosocial variables. Both unidimensional and multidimensional HRQOL instruments were acceptable; however, measurement strategies that examined single symptoms only (e.g., pain or nausea) were excluded.

Titles and abstracts of 2183 citations were identified from the MEDLINE searches. After duplicate citations and publications that did not report QOL data were eliminated, a total of 256 citations were identified that included HRQOL outcomes in breast cancer patients. Some of these reports addressed validation of HRQOL instruments, whereas others reported results of cross-sectional or observational studies. The latter were excluded from this review. A total of 66 citations that involved randomized clinical trials of treatment in breast cancer and that included self-reported HRQOL outcomes form the basis for this review.

Results of the Literature Search

The results of the literature search for citations meeting the above criteria are summarized in Table 1, which classifies reports by type of intervention, phase of the illness and its treatment, and year of publication (within a 5-year range). More than two-thirds of the reports (46 of 66) assessed biomedical interventions; approximately 40% of those (20 of 46) were conducted in patients with metastatic disease. Of the psychosocial interventions, 60% (12 of 20) were conducted in the adjuvant setting. The rate of publication of studies reporting HRQOL outcomes has increased in recent years, with approximately 70% (45 of 66) of the publications appearing since 1995. Given the time lag between study design and reporting, it is likely that there are a large number of ongoing studies whose results have yet to be reported.

The most commonly used HRQOL instruments are shown in Table 2 (other HRQOL instruments are listed in Tables 3–7). The instruments used in the biomedical intervention trials differed somewhat from those used in the psychosocial intervention trials. In the biomedical intervention trials, the EORTC QLQ-C30 *(2–5)* and the RSCL *(10,11)*, two cancer-specific HRQOL measures, were the most commonly used instruments. In the psychosocial intervention trials, the POMS *(8)*, a measure of mood, was the most commonly used instrument, followed by the CARES and the MOS-SF-36 *(9)*. Approximately 70% of the studies (46 of 66) used at least one of the nine most common (i.e., used in more than one study), well described, and validated HRQOL instruments listed in this table. Seventeen of the biomedical intervention trials used none of these instruments—some used other validated instruments designed specifically for the trial in question (this was most common in studies of primary management, symptom control, and metastatic disease); however, some used novel instruments with little documentation of validation (Tables 3–7), making interpretation and cross-study comparison of results difficult. The use of novel or unvalidated HRQOL instruments was less common in psychosocial intervention trials; none of these studies used such instruments as the only outcome measure.

Ideally, HRQOL instruments that are used in clinical trials should be sensitive (i.e., responsive) to change over time *(15)*. That is, HRQOL instruments that distinguish among groups of patients or that predict outcomes but that do not respond in a meaningful way to changes in underlying HRQOL are of little benefit in the clinical trial setting. Thus, instruments that measure state rather than trait characteristics and instruments that have scaling options that are sufficiently fine to allow for identification of improvement or deterioration in the attribute(s) being measured by the instrument are most likely to be useful in clinical trials. The nine HRQOL instruments shown in Table 2 have all been shown to be sensitive to changes in HRQOL in at least one clinical setting, although not all factors or subscales

Table 2. Summary of instruments used in randomized clinical trials of breast cancer treatment that included health-related qualify-of-life (HRQOL) measurement*

		Primary HRQOL instruments used†									
Type of randomized clinical trial	No. of studies	EORTC-QLQ-C-30 *(2–5)*	FLIC *(6)*	FACT-B *(7)*	POMS *(8)*	HADS *(9)*	RSCL *(10,11)*	CARES *(12)*	BCQ *(13)*	MOS-SF-36 *(14)*	Other (only)‡
Biomedical intervention											
Primary management	8	0	0	0	1	1	1	0	1	0	5
Adjuvant setting	7	2	0	0	0	1	0	0	2	1	2
Metastatic disease	20	8	2	0	0	1	5	0	0	0	6
Symptom control	8	1	1	0	0	2	2	0	0	0	3
Follow-up	3	1	1	0	1	1	0	0	0	1	1
Subtotal	46	12	4	0	2	6	8	0	3	2	17
Psychosocial intervention											
Adjuvant setting	12	0	1	2	6	2	1	2	0	2	3
Metastatic disease	7	1	1	0	6	0	0	0	0	0	0
Symptom control	1	0	0	0	0	0	0	1	0	1	0
Subtotal	20	1	2	2	12	2	1	3	0	3	3
Total	66	13	6	2	14	8	9	3	3	5	20

*EORTC-QLQ = European Organisation for Research and Treatment of Cancer Quality-of-Life (QOL) Questionnaire C-30; FLIC = Functional Living Index for Cancer; FACT-B = Functional Assessment of Cancer Therapy–Breast; POMS = Profile of Mood States; HADS = Hospital Anxiety and Depression Scale; RSCL = Rotterdam Symptom Checklist; CARES = Cancer Rehabilitation Scale; BCQ = Breast Cancer Chemotherapy Questionnaire; MOS-SF-36 = Medical Outcomes Study-Short Form 36.

†Some studies used more than one HRQOL instrument.

‡"Other" means that a variety of less common, sometimes unvalidated HRQOL instruments were used in these randomized clinical trials.

Table 3. Randomized clinical trials of primary management of breast cancer: surgery, radiation therapy, hormone therapy*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
de Haes et al. 1985 *(16)*, 1986 *(17)*	MRM vs. BCS + XRT	RSCL§ Five novel scales§	41	34	Yes	Yes	Yes	Body image better with BCS at 11 and 18 months (P<.01).	Not reported.	Yes
Kemeny et al. 1988 *(18)*	MRM vs. BCS vs. BCS + XRT	BSI§ Novel instrument	83	52	Yes	Yes	No	Multiple items better with BCS, including sexual and body image, psychological reaction and feelings, fear of recurrence.	Not reported.	Yes
Levy et al. 1989 *(19)*	MRM vs. BCS + XRT (NCI sample)	POMS§	93	—	No	Yes	Yes	No statistically significant differences.	Not reported.	Yes
Poulson et al. 1997 *(20)*	MRM vs. BCS + XRT	STAI§ LASA scales§	212	184	No	Yes	No	Body image (age 25–47 years) and sexuality (age 48–69 years) better with BCS (P<.05).	Full trial–no statistically significant difference.	Yes
Curran et al. 1998 *(21)*	MRM vs. BCS + XRT	Novel questionnaire§	902	278	Yes	Yes	Yes	Body image and satisfaction with treatment better with BCS (P = .001).	No statistically significant difference.	Yes
Whelan et al. 2000 *(22)*	BCS + XRT vs. BCS	BCQ§	837	720	Yes	Yes	Yes	Transiently worse overall HRQOL (P<.001), fatigue (P<.001), physical symptoms (P<.001), and inconvenience domains (P<.001) with XRT.	Reduced local recurrence with XRT (OR = 0.25, P<.001).	No
Wallace et al. 1993 *(23)*	XRT 40 Gy/15 fractions vs. 50 Gy/25 fractions	STAI§ HADS§ Health opinion survey	—	63	No	Yes	Yes	Transiently worse, weight gain, disruption of private life, and outlook on life in high-dose arm.	Not reported.	No
Bates et al. 1991 *(24)*	Tamoxifen vs. Tamoxifen + surgery	General health questionnaire§	381	237	Yes	No	No	No statistically significant difference.	Local control better with tamoxifen + surgery (P = .001).	No

*BCQ = Breast Cancer Chemotherapy Questionnaire; BCS = breast-conserving surgery; BSI = Brief Symptom Inventory; HADS = Hospital Anxiety and Depression Scale; HRQOL = health-related quality of life; LASA Scales = Linear Analog Self-Assessment Scales; MRM = modified radical mastectomy; NCI = National Cancer Institute; OR = odds ratio; POMS = Profile of Mood States; RSCL = Rotterdam Symptom Checklist; S/S = sample size; STAI = State–Trait Anxiety Inventory; XRT = radiation treatment; — = not stated.

†For "Missing data," "Statistical methods," and "Timing of HRQOL assessment," "Yes" means that the methodologic characteristic described in the text was satisfied and "No" means that the methodologic characteristic was not satisfied.

‡When only HRQOL outcomes (and not medical outcomes) were reported, "Yes" was entered.

§Validated questionnaire.

responded in a similar fashion. Furthermore, the ability of these instruments to detect small but clinically important changes is not clear. When sensitivity to clinically important change is not documented and when statistically significant effects of treatments on HRQOL are not identified, failure to detect effects of interventions on HRQOL must be interpreted with caution.

Summary of the Evidence

Details of the 66 randomized trials, including information on the key methodologic characteristics of each trial, are provided in Tables 3–7. Trial sample size refers to the total number of eligible patients in each study. HRQOL sample size is defined, when possible, as the number of patients who completed at least one HRQOL assessment, preferably the baseline assessment. At times, HRQOL sample size was derived from tables and figures (i.e., maximum number of respondents). With respect to missing data, any mention of the extent of missing data, even if limited to overall compliance, was classified as having adhered to the methodologic characteristic. Information on missing data was superficial for most trials and will be reviewed in detail in the

Table 4. Randomized clinical trials of adjuvant therapy for breast cancer: chemotherapy, hormone therapy*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Hurney et al. 1996 *(26)* IBCSG Trial VI	CMF × 3 vs. 6 cycles, then CMF × 3 vs. 0 cycles (re-induction) FACTORIAL Design	LASA scale PACIS§ Bf-S§	1475	1248	Yes	Yes	Yes	No differences at end of treatment (statistically significant heterogeneity during treatment).	Shorter DFS with CMF × 3 cycles.	No
Hurny et al. 1996 *(26)* IBCSG Trial VII	CMF 0 vs. 3 cycles early, then CMF 0 vs. 3 cycles delayed FACTORIAL Design (all received Tamoxifen)	LASA scale Bf-S§	1212	998	Yes	Yes	Yes	No differences at end of treatment (statistically significant heterogeneity during treatment).	Longer DFS with addition of CMF.	No
Levine et al. 1998 *(27)*	CEF vs. CMF	BCQ§	710	270	N/A	Yes	Yes	Overall HRQOL during treatment worse with CEF.	Longer DFS, OS ($P<.03$) with CEF.	No
van Dam et al. 1998 *(28)*	High-dose CXT with ABMT vs. conventional therapy	EORTC QLQ-C30§ Two Symptom Checklist Questionnaires§ Neuropsychologic Tests *(13)*	83	70	Yes	Yes	No	Overall HRQOL, physical, role, and social function worse with ABMT.	No statistically significant difference in RFS, OS; increased reversible toxicity with ABMT.	No
Fairclough et al. 1999 *(29)*	CAF × 6 months vs. 16-week intense regimen	BCQ§ qTWIST	646	163	Yes	Yes	Yes	Symptoms of fatigue transiently worse with 16 weeks treatment (BCQ); qTWIST better with CAF on shorter follow-up; better with 16 weeks on longer follow-up.	No statistically significant difference in DFS, OS; mixed toxicity results.	No
Curran et al. 2000 *(30)*	CEF vs. EC + G-CSF (LABC)	EORTC QLQ-C30§ EuroQol§ MOS-SF-36	448	403	Yes	Yes	Yes	Results depended on method of analysis; no difference in primary analysis (AUC); HRQOL better with CEF when summary measures used.	No statistically significant difference in PFS.	No
Nystedt et al. 2000 *(31)*	Tamoxifen (Y/N) Goserelin (Y/N) FACTORIAL Design	HADS§ Physical Symptoms and Problems List	194	149	Yes	Yes	Yes	Menopausal symptoms more intense and earlier with goserelin, later and milder with tamoxifen.	Longer time to first cancer event with goserelin.	No

*ABMT = autologous bone marrow transplant; AUC = area under the curve; BCQ = Breast Cancer Chemotherapy Questionnaire; Bf-S = Befindlichkeits-Skala questionnaire; CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; CEF = cyclophosphamide, epirubicin, 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CXT = chemotherapy; DFS = disease-free survival; EC = epirubicin, cyclophosphamide; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Qualify-of-Life Questionnaire C-30; G-CSF = granulocyte colony-stimulating factor; HADS = Hospital Anxiety and Depression Scale; HRQOL = health-related quality of life; IBCSG = International Breast Cancer Study Group; LABC = locally advanced breast cancer; LASA Scales = Linear Analog Self-Assessment Scales; MOS-SF-36 = Medical Outcomes Study Short Form 36; N/A = not applicable; OS = overall survival; PACIS = Perceived Adjustment to Chronic Illness Scale; PFS = progression-free survival; qTWIST = quality-adjusted time without symptoms; RFS = relapse-free survival; S/S = sample size; Y/N = yes/no.

†For "Missing data," "Statistical methods," and "Timing of HRQOL assessment," "Yes" means that the methodologic characteristic described in the text was satisfied and "No" means that the methodologic characteristic was not satisfied.

‡When only HRQOL outcomes (and not medical outcomes) were reported, "Yes" was entered.

§Validated questionnaire.

Table 5. Randomized clinical trials of therapy for metastatic breast cancer: chemotherapy, hormone therapy*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Coates et al. 1987 *(34)*	Continuous vs. intermittent chemotherapy	LASA scales§	305	133	Yes	Yes	Yes	QOL index, physical well-being, mood, and appetite better with continuous treatment.	Improved TTP with continuous treatment.	No
Tannock et al. 1988 *(35)*	Standard vs. low-dose CMF	LASA scales§	133	35‖	No	Yes	No	No statistically significant difference except alopecia worse with standard dose.	OS and RR better with standard dose. Increased alopecia and conjunctivitis with standard dose CMF.	No
Richards et al. 1992 *(36)*	Doxorubicin weekly vs. q3 weeks	RSCL§	59	55	Yes	Yes	Yes	Enhanced psychosocial status with q3 weekly treatment.	No statistically significant differences.	Yes/No
Fraser et al. 1993 *(37)*	CMF vs. epirubicin	NHP§ LASA scales§ Qualitator§	40	37	Yes	Yes	Yes	Transiently better pain and energy, and worse personal relationships with CMF at 3 months.	Improved TTF with CMF.	No
Bertsch et al. 1995 *(38)*	Vinorelbine vs. melphalan	Modified SWOG QOL instrument	179	179	No	Yes	Yes	Enhanced physical functioning with vinorelbine.	Improved TTP, TTF, OS with vinorelbine.	No
Buzdar et al. 1997 *(39)*	Anastrozole vs. Megace	RSCL§	386	142	No	Yes	Yes	Physical and psychologic scores transiently better with anastrozole.	No statistically significant difference in RR, TTP, TTF, OS; mixed toxicity profiles (especially weight).	Yes/No
Stewart et al. 1997 *(40)*	CAF vs. CNF	Priestman–Baum QOL	249	—	No	Yes	Yes	No statistically significant differences.	Better TTP, OS, RR with CAF.	No
Joensuu et al. 1998 *(41)*	Combination vs. single-agent chemotherapy	RSCL§	303	243	Yes	Yes	No	Physical functioning worse at 6 months with combination chemotherapy.	No statistically significant difference in RR, TTP, OS; combination chemotherapy more toxic.	No
Riccardi et al. 2000 *(42)*	120 FEC (120 mg/m^2)+ G-CSF vs. 60 FEC (60 mg/m^2)	EORTC QLQ-C30 + BR-23§	74	66	Yes	Yes	Yes	No statistically significant differences.	Improved TTP with 120 FEC (120 mg/m^2 epirubicin), but no difference in RR or OS.	No
Kloke et al. 1999 *(43)*	Maintenance Megace vs. no maintenance (after CXT)	Likert Scales (Coates)	90	37	Yes	Yes	No	No statistically significant differences.	Improved TTP, but no difference in OS with Megace; weight gain with Megace.	No

(Table continues)

Table 5 (continued). Randomized clinical trials of therapy for metastatic breast cancer: chemotherapy, hormone therapy*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Nabholtz et al. 1999 *(44)*	Docetaxel vs. mitomycin + vinblastine	EORTC QLQ-C30§	392	275	Yes	Yes	Yes	No difference in overall HRQOL; docetaxel better for nausea/vomiting and appetite; docetaxel worse for role and social functioning.	Improved RR, TTP, OS with docetaxel; increased toxicity with docetaxel.	No
Goss et al. 1999 *(45)*	Vorozole vs. Megace	FLIC§	452	138	No	Yes	No	No statistically significant differences.	No differences in TTP, RR, or OS; mixed toxicity effects.	No
Osoba et al. 1999 *(46)*	Herceptin + chemotherapy vs. chemotherapy	EORTC QLQ-C30§	469	431	Yes	Yes	Yes	No statistically significant differences.	Improved TTP with Herceptin.	No
Harper-Wynne et al. 1999 *(47)*	CMF vs. MM	RSCL§ HADS§	116	59	Yes	Yes	Yes	No statistically significant differences.	No statistically significant differences in TTP, RR, or OS.	No
Kornblith et al. 1993 *(48)*	Megace 160 mg vs. 800 mg vs. 1600 mg	FLIC§ Extra items	368	131	Yes	Yes	Yes	Low dose better on multiple scales (physical function, global QOL).	No difference in TTP or OS, but longer response duration with 160 mg; less toxicity with 160 mg.	No
Hakamies-Blomqvist et al. 2000 *(49)*	Docetaxel vs. MF	EORTC QLQ-C30§	283	245	Yes	Yes	Yes	Transient "minor" differences in HRQOL favoring MF.	Better RR and TTP, but greater toxicity with docetaxel.	No
Kramer et al. 2000 *(50)*	Paclitaxel vs. doxorubicin	EORTC QLQ-C30§ RSCL (6 items)	331	294¶	Yes	Yes	Yes	Mixed effect—different aspects of HRQOL better/worse with doxorubicin.	Better RR and PFS with doxorubicin; worse toxicity with doxorubicin.	No
Norris et al. 2000 *(51)*	Vinorelbine plus doxorubicin vs. doxorubicin	EORTC QLQ-C30§	303	197	Yes	Yes	Yes	No statistically significant differences.	No difference in RR, response duration, TTP, TTF, or OS; combination treatment more toxic.	No
Kaufmann et al. 2000 *(52)*	Exemestane vs. megestrol acetate	EORTC QLQ-C30§	769	—	No	Yes	No	Mixed results—global HRQOL better with exemestane.	Improved OS, duration of overall success, TTP, TTF with exemestane; mixed effects on symptoms/ toxicity.	No

(Table continues)

Table 5 (continued). Randomized clinical trials of therapy for metastatic breast cancer: chemotherapy, hormone therapy*

Trial characteristics			Methodologic characteristics				Trial outcomes			
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Buzdar et al. 2001 *(53)*	Letrozole 0.5 mg vs. 2.5 mg vs. megestrol acetate	EORTC QLQ-C30§	602	—	—	—	Yes	No statistically significant differences—no data presented.	Lower risk of progression; longer TTP and TTF, and OS on letrozole 0.5 mg; mixed toxicity.	No

*BR-23 = EORTC BR-23 Breast Module; CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CNF = cyclophosphamide, mitoxantrone, 5-fluorouracil; CXT = chemotherapy; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C-30; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; FLIC = Functional Living Index for Cancer; G-CSF = granulocyte colony-stimulating factor; HADS = Hospital Anxiety and Depression Scale; HRQOL = health-related quality of life; LASA Scales = Linear Analog Self-Assessment Scales; MF = methotrexate, 5-fluorouracil; MM = methotrexate, mitoxantrone; NHP = Nottingham Health Profile; OS = overall survival; PFS = progression-free survival; q3 weekly = treatment every 3 weeks; QOL = quality of life; RR = response rate; RSCL = Rotterdam Symptom Checklist; S/S = sample size; SWOG = Southwestern Oncology Group; TTF = time to treatment failure; TTP = time to progression; — = not reported.

†For "Missing data," "Statistical methods," and "Timing of HRQOL assessment," "Yes" means that the methodologic characteristic described in the text was satisfied and "No" means that the methodologic characteristic was not satisfied.

‡When only HRQOL outcomes (and not medical outcomes) were reported, "Yes" was entered. "Yes/No" was entered when it was not clear whether HRQOL influenced clinical decisions.

§Validated questionnaire.

‖HRQOL data available in 49 patients; only 35 patients were included in the analysis.

¶Of the 294 eligible patients, 180 completed baseline HRQOL questionnaires.

following sections. Adequate reporting of timing of HRQOL assessments required that the trial report the precise pre-trial definition of the time intervals between HRQOL evaluations. Any report of the statistical methods used to analyze HRQOL data was classified as having adhered to the methodologic characteristic. In most studies, HRQOL outcome was a secondary end point, and precise methods for data collection and quality control were rarely stated. These methodologic standards were applied independently by two of the authors (P. J. Goodwin, L. J. Bordeleau); disagreements were resolved by discussion.

Tables 3–7 also include a brief description of the intervention(s) studied, the HRQOL instruments used, the medical and HRQOL outcomes as reported by the investigators, and an assessment of whether the information obtained from HRQOL measurement in the trial influenced clinical decision making regarding the use of the intervention under investigation. In this review, we have not performed a quantitative meta-analysis; instead, we have focused on the extent to which the measurement of HRQOL contributed qualitatively to clinical decision making (i.e., to selection of the optimal treatment among those treatments being studied) in this group of randomized clinical trials.

Primary Management: Surgery, Radiation Therapy, Hormone Therapy

Eight randomized clinical trials evaluated HRQOL in the primary management of breast cancer (Table 3). Five *(16–21)* of these studies compared mastectomy with breast-conserving surgery (BCS) plus radiation treatment (XRT). All but three *(19,20,23)* of the eight studies provided information on overall rate of missing HRQOL questionnaires. The rate of missing items *(21)* and the reasons for missing data *(16)* were provided in one study each. The five studies that compared mastectomy with BCS plus XRT used a variety of psychosocial questionnaires. Two of these studies also included medical outcomes *(20,21)*; neither identified a statistically significant difference in recurrence or survival rates, in keeping with other published studies *(25)*. Four studies *(17,18,20,21)* identified at least one aspect of body image (including emotional reaction to, or satisfaction with, body image) that was better in women undergoing BCS plus XRT than in women undergoing mastectomy. One study *(20)* reported an improvement in sexual activity among older (but not younger) women receiving BCS plus XRT, whereas another study *(21)* reported that women who underwent BCS plus XRT were more satisfied with their treatment than women who underwent mastectomy. One study *(18)* identified a range of psychological reactions (i.e., feelings and concerns) that were better in women undergoing BCS plus XRT than in women undergoing mastectomy, but this study did not use a well-validated HRQOL instrument to measure these reactions.

The equivalence of BCS combined with radiation to mastectomy with respect to distant recurrence and survival is now widely accepted *(25)*. Although it may seem obvious that, in terms of HRQOL, BCS would be the preferred treatment option over mastectomy, demonstration of enhanced satisfaction with body image, of enhanced sexual functioning, and of enhanced psychological status after BCS provides an empiric foundation for this conclusion *(17,18,20,21)*. However, the finding that not all aspects of HRQOL were better in patients undergoing BCS, coupled with a failure of these studies to identify overall differences in HRQOL, suggests that, for individual women, mastectomy may remain a reasonable alternative. Although some nonrandomized studies have suggested an increased fear of recurrence after BCS, reduction in this fear after BCS was documented in one of the randomized trials *(18)* studied here.

The remaining three studies *(22–24)* that evaluated HRQOL in the primary management of breast cancer included a report comparing BCS with and without radiation *(22)*, which demon-

Table 6. Randomized clinical trials of symptom control/supportive care and follow-up in breast cancer*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Soukop et al. 1992 *(54)*	Ondansetron vs. metoclopramide	RSCL§	187	184	Yes	Yes	Yes	Better psychological status with ondansetron.	Reduced emesis and nausea with ondansetron.	No
Clavel et al. 1993 *(55)*	Ondansetron vs. metoclopramide	RSCL§	183	—	No	No	Yes	Better psychological status with ondansetron.	Reduced emesis with ondansetron.	No
Clavel et al. 1993 *(55)*	Ondansetron vs. alizapride	FLIC§ FLIE§	252	—	No	No	Yes	FLIE scores better with ondansetron.	Reduced emesis with ondansetron.	No
Razavi et al. 1993 *(56)*	Alprazolam vs. placebo (both with psychologic support)	HADS§ SCL-90R§ MADRS HAS MANE RS§	57	57	No	Yes	Yes	No statistically significant difference.	Lower anticipatory nausea at second visit with alprazolam.	No
Holton-Verzantvoort et al. 1991 *(57)*	Pamidronate vs. no treatment	Unique questionnaire§ with four subscales	167	144	Yes	Yes	Yes	Better mobility and less bone pain with pamidronate on HRQOL questionnaire.	Lower hypercalcemia, bone pain, pathologic fractures, and radiation treatment complications with pamidronate.	No
Hultborn et al. 1999 *(58)*	Pamidronate vs. placebo	LASA Scales§	404	—	No	Yes	Yes	No statistically significant difference.	Pamidronate lowered skeletal events, time to pain progression or hypercalcemic events with pamidronate.	No
Kristensen et al. 1999 *(59)*	Clodronate vs. no intervention	EORTC QLQ-C30§ HADS§	100	62	Yes	Yes	Yes	No statistically significant difference.	Reduced skeletal events, time to first skeletal event, fractures, and need for radiotherapy.	No
Pandya et al. 2000 *(60)*	Clonidine vs. placebo	Hot Flash Diary Symptom Checklist QOL 10-Point Scale	194	194	Yes	Yes	Yes	HRQOL transiently better with clonidine.	Hot flash frequency better with clonidine; insomnia worse with clonidine.	No
Dixon et al. 1993 *(61)*	CT vs. MRI of axilla	QALY tool kit§	57	37‖	Yes	Yes	Yes	No statistically significant difference.	No statistically significant difference in PPV and NPV.	No
GIVIO 1994 *(62)*	Intensive surveillance vs. physician visits	POMS§ FLIC§ SIP§ CIPS§	1320	—	Yes	Yes	Yes	No statistically significant difference.	No statistically significant difference.	No

(Table continues)

Table 6 (continued). Randomized clinical trials of symptom control/supportive care and follow-up in breast cancer*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Grunfeld et al. 1996 *(63)*	Hospital vs. general practice follow-up	EORTC QLQ-C30§ MOS-SF-36§ HADS§	296	288	Yes	Yes	Yes	Transient worsening in anxiety and depression mid-trial in general practice group (not statistically significant).	No statistically significant difference in recurrence rate or time to diagnosis of recurrence.	No

*CIPS = Cancer Inventory of Problem Situation; CT = computerized tomography; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C-30; FLIC = Functional Living Index for Cancer; FLIE = Functional Living Index–Emesis; HADS = Hospital Anxiety and Depression Scale; HAS = Hamilton Anxiety Scale; HRQOL = health-related quality of life; LASA Scales = Linear Analog Self-Assessment Scales; MADRS = Montgomery and Asberg Depression Rating Scale; MANE = Morrow Assessment for Nausea and Emesis; MOS-SF-36 = Medical Outcomes Study Short Form 36; MRI = magnetic resonance imaging; NPV = negative predictive value; POMS = Profile of Mood States; PPV = positive predictive value; QALY = quality-adjusted life year; QOL = quality of life; RS = Repression-Sensitization Scale (revised); RSCL = Rotterdam Symptom Checklist; S/S = sample size; SCL-90R = Symptom Checklist-90 (revised); SIP = Sickness Impact Profile; — = not reported.

†For "Missing data," "Statistical methods," and "Timing of HRQOL assessment," "Yes" means that the methodologic characteristic described in the text was satisfied and "No" = means that the methodologic characteristic was not satisfied.

‡When only HRQOL outcomes (and not medical outcomes) were reported, "Yes" was entered.

§Validated questionnaire.

‖Overall S/S = 57; complete results in 37 patients.

strated a transient worsening in HRQOL during radiation treatment. Nevertheless, radiation reduced local recurrence without influencing overall survival (OS), and the authors of the study recommended that radiation be used. Another report *(23)* examined different radiation dose and fractionation schedules without reporting medical outcomes. The higher dose regimen (i.e., 50 gray (Gy)/25 fractions) was associated with more weight gain, disruption of private life, and a less positive outlook on life at the completion of treatment than the lower dose regimen (i.e., 40 Gy/15 fractions), but no differences in these HRQOL measures were present 6 months later. A final study *(24)* examined the role of surgery in elderly women receiving tamoxifen for primary breast cancer. Although local control was better when surgery was used than when surgery was not used, no differences in HRQOL were seen.

In summary, in studies of primary management of breast cancer, HRQOL measurement provided information that was useful in selecting optimal treatment when two medical treatments were demonstrated to have equivalent medical outcomes; that is, demonstration of enhanced HRQOL (particularly body image) with BCS and with lower dose radiation can help guide treatment recommendations.

Adjuvant Therapy: Chemotherapy, Hormone Therapy

A surprisingly small number of published studies (n = 7) of adjuvant therapy of breast cancer patients have included HRQOL outcomes (Table 4). There are likely to be additional ongoing adjuvant studies that have measured HRQOL outcomes that have not yet been published because recurrence and survival data are not mature. It is also possible that HRQOL outcomes in some trials were not reported for those trials in which enhanced survival in one treatment arm led to treatment recommendations. Two of the published studies *(27,29)* reviewed here used the BCQ, two *(28,30)* used the EORTC QLQ-C30, and two *(26)* used a trio of instruments (linear analog self-assessment scales [LASA Scales], Perceived Adjustment to Chronic Illness Scale [PACIS], and Befindlichkeits-Skala questionnaire [Bf-S]) that have undergone some validation but have not been commonly used. As can be seen in Table 4, HRQOL measurements were often performed on a subset of patients. All but one study *(26,28–31)* provided information on the overall rate of missing HRQOL questionnaires (none provided information on missing questionnaire items); the remaining study *(27)* limited the analysis of HRQOL to complete cases. Reasons for missing data were addressed in three studies *(29–31)*. All studies reported methods of statistical analysis, and all but one *(28)* reported timing of HRQOL assessment.

In general, use of chemotherapy, especially more aggressive chemotherapy, was associated with worse HRQOL than was seen with hormonal interventions or less aggressive chemotherapy. However, the effects on HRQOL were often transient, occurring during treatment but resolving after treatment was completed *(26,27,29)*. In a trial of goserelin and tamoxifen *(31)*, some aspects of HRQOL were found to be worse with goserelin, others to be worse with tamoxifen, and some to be similar regardless of treatment. Two reports *(29,30)* evaluated HRQOL using more than one instrument or approach to analysis. One report *(29)* found that use of the BCQ versus the quality-adjusted time without symptoms (q-TWIST) instrument, essentially a utility-based measurement, yielded HRQOL effects that were in opposite directions. In the other report *(30)*, a detailed analysis found that the HRQOL effects depended on the statistical approach used, with no differences in HRQOL between the treatments being seen when area under the curve or time-to-minimum or time-to-maximum scores were used, but enhanced HRQOL for one treatment when mean, median, and minimum summary measures were used. These thoughtful analyses highlight the need for research to understand the meaning of results obtained using different HRQOL instruments and to evaluate different approaches to statistical analysis. These issues have been explored extensively in *Statistics in Medicine (32)*.

Because the ultimate goal of adjuvant treatment is to improve long-term survival, short-term toxicity is often accepted. Only if

Table 7. Randomized clinical trials of psychosocial interventions in breast cancer; adjuvant setting (A), metastatic setting (M), symptom control/supportive care, and follow-up (S)*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Setting/ interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Christensen 1983 *(66)*	Couple counseling vs. no interpretation (A)	BDI§ STAI§ RSES§ Others	20	20	Yes	Yes	Yes	No overall effects.	None reported.	Yes
Bridge et al. 1988 *(67)*	Relaxation group vs. relaxation plus imagery group vs. attention control (A)	POMS§ Leeds General Scales Questionnaire (anxiety, depression)	154	139	Yes	Yes	Yes	Enhanced mood with intervention (relaxation plus imagery best).	None reported.	Yes
Maunsell et al. 1996 *(68)*	Telephone screening and intervention vs. usual care (A)	Psychiatric Symptom Index§ Others	261	250	Yes	Yes	Yes	No statistically significant differences.	None reported.	Yes
Marchioro et al. 1996 *(69)*	Individual cognitive psychotherapy and family counseling vs. usual care (A)	BDI§ FLIC§ 16-PF (A) IIQ	36	36	No	Yes	Yes	Reduced depression and enhanced HRQOL with intervention.	None reported.	Yes
Richardson et al. 1997 *(70)*	Support group × 6 weeks vs. relaxation/ imagery group × 6 weeks vs. standard care (A)	FACT-B§ POMS-B§ WOC-CA§ DUFSS§	47	47	Yes	Yes	No	Improved coping skills, greater acceptance of death in support groups; increased amount of seeking support from others in both treatment groups.	No difference in immune function.	Yes
Wengström et al. 1997 *(71)*	Nursing intervention (individual) vs. nil (A)	IES CARES-sf Others	134	134	Yes	Yes	Yes	Intervention reduced stress reactions.	None reported.	Yes
Ritz et al. 2000 *(72)*	Advanced practice nursing interventions (individual) vs. nil (A)	FACT-B§ POMS§ MUIS§	210	210	Yes	Yes	Yes	Intervention reduced uncertainty at 1, 3, and 6, but not 12 months.	None reported.	Yes
Sandgren et al. 2000 *(73)*	Telephone counseling vs. assessment only (A)	POMS§ MOS-SF-36§ CRI-R Stress Q	62	53	Yes	Yes	Yes	Greater use of nursing help-line by counseled women.	None reported.	Yes
Fogarty et al. 1999 *(74)*	Enhanced compassion vs. standard video tape (A)	STAI-S§	123	123	No	No	Yes	Reduced anxiety with enhanced compassion type.	Not reported.	Yes

(Table continues)

Table 7 (continued). Randomized clinical trials of psychosocial interventions in breast cancer; adjuvant setting (A), metastatic setting (M), symptom control/supportive care, and follow-up (S)*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Setting/ interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Bultz et al. 2000 *(75)*‖	Psychoeducational group (partners) vs. nil (A)	POMS§ MAC§ DUFSS§ IMS	34	34	Yes	Yes	Yes	No differences.	None reported.	Yes
Fukui et al. 2000 *(76)*	Group intervention vs. nil (A)	POMS§ MAC§ HADS§	50	50	Yes	Yes	Yes	Improved mood, vigor, and fighting spirit with intervention.	None reported.	Yes
Helgeson et al. 2001 *(77)*	Education and peer discussion vs. education vs. peer discussion (all group interventions) vs. nil (A)	MOS-SF-36§ IES§ CARES§ RSES§ PNAS§	312	258	No	Yes	Yes	Education (not peer discussion) improved vitality, social functioning, mental health, bodily pain.	None reported.	Yes
Walker et al. 1999 *(78)*	Relaxation/ imagery vs. control (locally advanced) (A)	RSCL§ HADS§ CECS§ MRS§ GQOL Others	96	96	Yes	Yes	Yes	Improved emotional control, HRQOL, and relaxation with intervention.	No difference in response rates.	Yes
Spiegel et al. 1981 *(79)*, 1983 *(80)*, 1989 *(87)*	Supportive-expressive group therapy vs. nil (M)	POMS§ Unique pain scales	86	64	Yes	Yes	No	Improved mood, reduced pain, with intervention.	Prolonged survival in intervention group.	No
Arathuzik 1994 *(81)*	Relaxation/ visualization vs. above plus cognitive-behavioral therapy vs. control (M)	POMS-B§ Johnson Pain Scale§	24	24	Yes	Yes	Yes	Both interventions enhanced perceived ability to decrease pain.	None reported.	Yes
Edmonds et al. 1998 *(82)*	Group support with cognitive-behavioral therapy vs. home study (M)	POMS§ FLIC§ MAC§ Others	66	66	Yes	Yes	Yes	No differences.	No difference in survival.	Yes
Edelman et al. 1999 *(83)*	Cognitive-behavioral group × 6 weeks vs. nil (M)	POMS§ CSI§	124	92	Yes	Yes	Yes	Intervention improved self-esteem and depression; did not persist after intervention ended.	No difference in survival.	Yes
Classen et al. 2001 *(84)*	Supportive-expressive group therapy vs. nil (M)	POMS§ IES§	125	102	Yes	Yes	Yes	Reduced stress response with intervention.	Pending.	Yes
Goodwin et al. 2001 *(85)*	Supportive-expressive group therapy vs. nil (M)	POMS§ Pain LASA Scales EORTC QLQ-C30	235	218	Yes	Yes	Yes	Enhanced mood, reduced pain with intervention, but no change in HRQOL.	No difference in survival.	Yes

(Table continues)

Table 7 (continued). Randomized clinical trials of psychosocial interventions in breast cancer; adjuvant setting (A), metastatic setting (M), symptom control/supportive care, and follow-up (S)*

Trial characteristics			Methodologic characteristics					Trial outcomes		
Reference	Setting/ interventions	Instruments	Trial S/S	HRQOL S/S	Missing data†	Statistical methods†	Timing of HRQOL assessment†	HRQOL outcome	Medical outcome	HRQOL influenced clinical decision?‡
Ganz et al. 2000 *(86)*	Comprehensive menopausal assessment vs. nil (S)	CARES§ MOS-SF-36§ Menopausal Symptom Scale	76	72	Yes	Yes	Yes	Enhanced sexual functioning, vitality; reduced menopausal symptoms with intervention.	None reported.	Yes

*16-PF (A) = Personality Questionnaire; BDI = Beck Depression Inventory; CARES-sf = Cancer Rehabilitation Scale (short form); CECS = Courtauld Emotional Control Scale; CRI-R = Coping Response Indices-Revised; CSI = Coopersmith Self-Esteem Inventory; DUFSS = Duke University of North Carolina Social Support Questionnaire; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C-30; FACT-B = Functional Assessment of Cancer Therapy-Breast; FLIC = Functional Living Index for Cancer; GQOL = Global Quality of Life; HADS = Hospital Anxiety and Depression Scale; HRQOL = health-related quality of life; IES = Impact of Events Scale; IIQ = Interx Introject Questionnaire; IMS = Index of Marital Satisfaction; LASA Scales = Linear Analog Self-Assessment Scales; MAC = Mental Adjustment to Cancer Scale; MOS-SF-36 = Medical Outcomes Study Short Form 36; MRS = Mood Rating Scale; MUIS = Mishell Uncertainty of Illness Scale; Pain LASA Scale = Pain Linear Analog Self-Assessment Scale; PNAS = Positive and Negative Affect Scale; POMS = Profile of Mood States; POMS-B = Profile of Mood States (brief version); RSCL = Rotterdam Symptom Checklist; RSES = Rosenberg Self-Esteem Scale; S/S = sample size; STAI-S = State-Trait Anxiety Scale (self-report); WOC-CA = Ways of Coping-Cancer.

†For "Missing data," "Statistical methods," and "Timing of HRQOL assessment," "Yes" means that the methodologic characteristic described in the text was satisfied; "No" means that the methodologic characteristic was not satisfied.

‡When only HRQOL outcomes (and not medical outcomes) were reported. "Yes" was entered.

§Validated questionnaire.

‖Authors consider intervention beneficial even though all $P>.05$.

adjuvant treatments are shown to have equivalent effects on recurrence and survival is it likely that transient HRQOL effects will influence treatment decisions. It can be seen from Table 4 that this was the case for the trials reviewed here. In general, HRQOL effects were either absent, transient, or associated with observed toxicity. In only one study *(31)* did HRQOL data provide potentially important information that was not available using traditional medical outcomes. The Physical Symptoms and Problem List used in the trial of goserelin and tamoxifen identified greater toxicity with goserelin *(31)*. This questionnaire was more focused on symptoms and less on functioning than most HRQOL instruments, and it is arguable that much of the information obtained from it could have been obtained by collecting toxicity data. Furthermore, if the longer time to first cancer event in women receiving goserelin persists with longer follow-up, these HRQOL results, which indicate greater toxicity with goserelin, will probably not play an important role in treatment decisions, and goserelin will be recommended as the optimal treatment.

In summary, in the adjuvant setting, where the goal of treatment is to delay recurrence and/or prolong survival, information obtained using HRQOL measures has had little impact on clinical decision making. It is possible that long-term HRQOL assessments addressing potential late toxicities (e.g., cognitive functioning, menopause) or results of completed and/or ongoing studies that have yet to be reported may provide a different perspective on the contribution of HRQOL measurement to selection of optimal treatment in the adjuvant setting. This question should be explored in future research *(33)*.

Metastatic Disease: Chemotherapy, Hormone Therapy

The metastatic setting has given rise to the largest single group of HRQOL trials in breast cancer (Table 5). We examined 20 such trials. Measurement of HRQOL in these studies was at times limited to a small number of items. A range of HRQOL instruments was used in these studies, the most common being the EORTC QLQ-C30 and the RSCL. Six trials *(34,35,37,38,40, 43)* used instruments that were relatively uncommon or that had been modified specifically for the study; some evidence of validity was available for most of these instruments. Thirteen studies *(34,36,37,41–44,46–51)* provided information on the overall rate of missing HRQOL questionnaires. The rate of missing items was reported in two studies *(41,49)*, and reasons for missing data were provided in eight *(36,37,42,44,47–50)*. Missing data were often substantial, leading to concern about poor generalizability and bias in HRQOL results *(32)*. Most of these studies provided information on statistical methods of analysis and on timing of HRQOL measurements.

In the majority of these studies, there were statistically significant differences in HRQOL between study arms. However, these differences were usually not present for all items and/or subscales on the instruments used and, in some studies *(44,50,52)*, differences in HRQOL on some scales were in opposite directions to those on other scales, making interpretation difficult. There was no consistent pattern to the domains influenced by treatment—i.e., pain, physical, psychological, social, interpersonal, and symptom scales or items all yielded statistically significant differences between study arms in at least one study. Furthermore, differences in HRQOL scores were sometimes seen at one time point in the trial and not at other time points *(39,49,50)*. Some studies that reported no statistically significant HRQOL effects were small [e.g., *(43)*] or commented that statistical power was inadequate to detect a clinically important difference in HRQOL between study arms *(47)*. Low power, insensitivity of instruments (or specific domains) to change, or use of instruments that did not include domains likely

to be influenced by the interventions being studied may have contributed to some of the lack of statistically significant HRQOL differences between study arms in these studies.

The goal of treatment in metastatic breast cancer has traditionally been palliation of symptoms, although the introduction of promising new agents in the last decade has led to studies in which survival benefits are sought. Disappointingly, HRQOL outcomes in these studies have provided little additional information beyond that obtained from traditional medical outcomes (including toxicity). In one study *(34)*, evidence of HRQOL benefits was present earlier than evidence of medical benefits; however, the identification of improvement in time to disease progression with continuous (as opposed to intermittent) chemotherapy was the key factor leading to selection of continuous treatment as the preferred approach. Another study *(39)* reported enhanced physical and psychological scores on the RSCL questionnaire for patients receiving anastrozole over patients receiving megestrol acetate in the absence of statistically significant effects on response rate, time to disease progression, or time to treatment failure. Some treatment toxicities were greater with anastrozole than with megestrol acetate treatment, and others, notably weight gain, were less. Given the equivalent medical outcomes of this study, the enhanced HRQOL in patients receiving anastrozole provides support for its selection as the preferred treatment; however, the association of anastrozole with reduced weight gain was probably sufficient to guide this selection. In a final study *(36)*, weekly doxorubicin was compared with doxorubicin administered every 3 weeks. No differences in medical outcomes or toxicity were identified; however, patients receiving 3-weekly therapy had better scores than those receiving weekly therapy on the psychological subscale of the RSCL at the midpoint of treatment but not at the end. Although the simpler logistics of 3-weekly administration of doxorubicin would probably be the most important determinant of treatment decisions in this situation, a transient psychological benefit provides additional support for such a decision.

Given the findings discussed above, the routine use of HRQOL measurement in randomized drug trials in metastatic breast cancer may not be warranted unless one or more of the agents being tested has very modest or differing toxicities that could have an effect on HRQOL. In none of the published studies reviewed here did HRQOL measurement provide information that had a clear effect on treatment recommendations. Careful measurement of toxicity and performance status, coupled with measures of tumor response and/or survival, usually provided sufficient information for treatment decisions. When treatments have equivalent tumor-related outcomes and competing toxicities are present or the logistics of treatment administration differ, as was the case in the two trials discussed above *(36,39)*, then HRQOL measurement may help to shift the balance in favor of one treatment over another. However, HRQOL measurement could probably be deferred to a follow-up trial in the rare situations in which one of these scenarios occurs.

Symptom Control/Supportive Care and Follow-up

Eight randomized trials of symptom control/supportive care *(54–60)* and three trials of different approaches to investigation or follow-up of breast cancer patients *(61–63)* have included HRQOL outcomes (Table 6). HRQOL measurements were often performed in a subset of patients in these trials. Seven trials *(54,57,59–63)* provided information on overall rate of missing HRQOL questionnaires, but none reported the extent of missing items or the reasons for missing data. Two trials *(55)* provided no information on their statistical methods. Four of the symptom control trials *(54–56)* investigated chemotherapy-associated nausea using standard HRQOL instruments, including the RSCL, HADS, and FLIC. Ondansetron was shown to reduce emesis in three *(54,55)* of these trials using emesis questionnaires or diaries. All three trials identified enhancement of at least one aspect of HRQOL by ondansetron. In a study by Razavi et al. *(56)* that evaluated alprazolam versus placebo to treat nausea and vomiting, no HRQOL effect was identified, although anticipatory nausea was improved. The use of bisphosphonates (e.g., pamidronate and clodronate) in breast cancer metastatic to bone was evaluated in three trials *(57–59)* using a variety of self-report HRQOL instruments [two additional studies *(64,65)* were excluded from this review because they used the Spitzer QOL Index, which is observer, not patient, reported]. All of these trials of bisphosphonates identified important beneficial effects of using bisphosphonates on fracture rates, pain, hypercalcemia, and/or the use of radiation. One of the studies *(57)*, which used a novel HRQOL instrument that had been developed specifically for the trial, reported that HRQOL was better in patients treated with bisphosphonates than in patients treated with placebo. In a symptom control trial *(60)*, clonidine reduced hot flashes and improved HRQOL. Thus, when HRQOL outcomes were statistically significant, they were consistent with medical outcomes in these trials, and they also provided support for therapeutic decisions based on these medical outcomes. However, HRQOL outcomes were often not statistically significant in the presence of statistically significant medical outcomes.

The three follow-up trials *(61–63)* used a variety of questionnaires: EORTC QLQ-C30, MOS-SF-36, HADS, and POMS. In a trial comparing hospital-based with general practice-based follow-up *(63)*, change in the mean anxiety and depression score from baseline was transiently worse in the general practice group at midtrial compared with the hospital group; however, the magnitude of the change was small, and there were no statistically significant between-group differences. No other statistically significant medical, psychosocial, or HRQOL outcomes were reported in these trials.

Taken together, the results of these symptom control/supportive care and follow-up studies suggest that measurement of HRQOL adds little if any benefit to traditional medical outcomes in these trials. The use of very focused measures of symptoms (e.g., pain, nausea), may have made general HRQOL measures redundant. However, it is disappointing to note that in two trials of bisphosphonates *(58,59)*, HRQOL instruments failed to identify benefits of bisphosphonates that were readily apparent when traditional medical outcome measures were used. It might be argued that pain and nausea self-report measures are HRQOL measures; however, because they are unidimensional and do not measure function, we have not included them as traditional HRQOL measures. Unidimensional measures serve a purpose in studies of symptom control, however, and by focusing on those symptoms most likely to be influenced by treatment, they allow an evaluation of symptoms that is both more detailed and less burdensome than a general HRQOL measure would be. Thus, planners of symptom control studies might do well to select simple instruments that focus on the specific symptoms being

studied rather than selecting general or even cancer-specific HRQOL instruments.

Given the absence of benefit with any outcome (i.e., medical or HRQOL) in the follow-up trials, it is difficult to draw conclusions about the potential contribution of HRQOL measurement in this setting. Low statistical power or a true lack of effectiveness of the interventions studied may have led to these negative results. Further research into a potential role for HRQOL measurements in trials using other (effective) interventions and/or larger sample sizes is clearly needed.

Psychosocial Interventions: Adjuvant, Metastatic, Symptom Control

The psychosocial intervention studies (Table 7) were conducted in the adjuvant, metastatic, and symptom control settings. Eleven trials *(67–74,76–78)* in the adjuvant setting involved breast cancer patients, one trial *(75)* involved partners of breast cancer patients, and one trial *(66)* involved breast cancer patients and their spouses. The interventions ranged from support groups *(67,70,76,77)*, to individual or couple counseling *(66,69,71)*, to relaxation training *(67,70,78)*, to telephone counseling or screening *(68,73)*. The most commonly used HRQOL instruments included the POMS, which was used in six studies, and multidimensional HRQOL instruments (i.e., FACT-B, FLIC, RSCL, and CARES), which were also used in six studies; other instruments included unidimensional measures drawn from the field of psychiatry (e.g., HADS and STAI). HRQOL measurements were available for all patients in most of the studies. The rate of missing HRQOL questionnaires was addressed to differing extents in all of these studies, but none reported missing items. Most studies provided information on statistical methods of analysis and on timing of HRQOL measurement. Only two of the adjuvant studies reported medical outcomes—immune parameters in one *(70)* and clinical or pathologic response to neoadjuvant therapy in the other *(78)*. Neither medical outcome was influenced by the psychosocial intervention.

Psychosocial benefits were identified in 10 adjuvant studies *(67,69–74,76–78)* (Table 7). Relaxation plus imagery improved mood (POMS) compared with relaxation alone or a control condition *(67)*, whereas individual cognitive psychotherapy with family counseling improved depression and HRQOL *(69)*. A 6- *(70)* or 8-week *(77)* support or educational group enhanced overall coping skills *(70)*, social functioning, and mental health *(77)*, whereas relaxation training plus imagery resulted in greater emotional control, improved mood, and relaxation *(78)* compared with a control group. Two nursing interventions reduced uncertainty *(72)* or stress reactions *(71)*, and individuals who watched an enhanced compassion videotape experienced less anxiety than those who watched a standard videotape *(74)*. Finally, women participating in a 6-week structured group intervention experienced improved mood and had increased vigor and enhanced use of a fighting spirit coping style *(76)*.

Interest in psychosocial interventions in metastatic breast cancer was stimulated by an early report that supportive–expressive group therapy improved mood, reduced suffering from pain, and improved survival *(79,80,87)*. Five subsequent trials in this setting were identified *(81–85)*. All of these trials used the POMS and other psychological questionnaires; two also used more general HRQOL measures *(82,85)*. The three trials that examined survival *(82,83,85)* failed to identify statistically significant effects of the intervention. Survival results are not yet mature in a fourth trial *(84)*. One trial *(83)* evaluated a 6-week cognitive-behavioral group intervention that identified beneficial effects on mood and self-esteem at its conclusion, but these benefits did not persist 3 or 6 months later. Another trial *(85)* reported enhanced mood and reduced pain but no change in HRQOL in women participating in long-term supportive–expressive group therapy. Symptoms of post-traumatic stress disorder were reduced in women receiving supportive–expressive group therapy *(84)*, and perceived ability to reduce pain was enhanced through the use of a relaxation–visualization intervention *(81)*.

The only psychosocial intervention trial focusing on symptom control *(86)* studied the use of a comprehensive menopausal assessment (symptom assessment, education, counseling and, as appropriate, specific pharmacologic and behavioral intervention) in healthy breast cancer survivors. Beneficial effects of the assessment, including the pharmacologic and behavioral interventions, were identified using subscales of both the CARES and the MOS-SF-36 instruments, consistent with improved menopausal symptoms identified using the Menopausal Symptom Scale.

Improvement in at least one psychosocial or HRQOL outcome was identified in the majority of the psychosocial intervention studies. In general, psychosocial interventions resulted in enhanced psychosocial functioning. Improvements in HRQOL were often identified with one psychosocial instrument but not with others, or in one subscale of an instrument but not in others, making interpretation of results difficult. In addition, these studies were less likely than studies of biomedical interventions to include multidimensional HRQOL measures; among the eight studies that did *(69,70,72,73,78,82,85,86)*, statistically significant effects were identified in only two trials *(77,86)*. Thus, it is important to tailor the selection of HRQOL and psychosocial instruments to the specific intervention being evaluated to ensure that outcomes (i.e., both psychosocial and HRQOL) likely to be influenced by the intervention are captured and to not rely solely on general or cancer-specific HRQOL instruments to identify treatment effects.

Although there has been considerable interest in the effect of psychosocial interventions on survival in breast cancer, a statistically significant effect was seen only in the original study of Spiegel et al. *(87)*. It is probably more reasonable to expect that psychosocial interventions would have an impact on psychosocial functioning and/or HRQOL outcomes. As a result, it would be anticipated that HRQOL outcomes would play an important role in guiding treatment recommendations in studies of psychosocial interventions. As can be seen in Table 7, HRQOL outcomes did influence clinical decision making in all but one *(79, 80,87)* of the psychosocial intervention trials reviewed here.

Discussion

This review has identified several areas of inquiry where adding an assessment of HRQOL to randomized clinical trials in breast cancer contributes little to clinical decision making about treatment alternatives. This conclusion is particularly true when biomedical interventions are being evaluated. This result may reflect the lack of precision of the currently available HRQOL instruments (i.e., the dimensions measured are scaled too coarsely to detect changes or differences that matter to patients), the failure of existing instruments to capture important domains (e.g., cognitive functioning), or the ability of simpler measure-

ments (e.g., toxicity) to provide similar information. However, it may also be that HRQOL outcomes are of secondary importance when medical outcomes, particularly survival, are statistically significantly affected by treatment. It is clear that when a treatment is medically superior to another, most patients will desire that treatment, even if there may be an increase in short-term toxicity *(88)*. Conversely, if treatments have equivalent medical outcomes, then differences in toxicity and HRQOL may be important. Perhaps HRQOL measures should be included in randomized biomedical treatment trials only when equivalency of treatments is likely and when differences in HRQOL will, therefore, become the primary factor influencing treatment decisions.

Other issues that are of increasing interest, given the growing number of long-term breast cancer survivors, are the long-term, late effects associated with adjuvant therapy. These long-term effects are particularly relevant to patients with small tumors who receive increasingly complex and intensive therapy and whose likelihood of long-term survival is high *(89,90)*. Studies of long-term, late HRQOL effects are often attached to large randomized adjuvant therapy trials in which specific treatments and doses can be evaluated for their late effects; however, the inclusion of HRQOL outcome measures should be undertaken with specific hypotheses in mind. Investigators may opt instead to perform observational studies. Regardless of the study design used, HRQOL instruments selected for outcome measurement should include domains that are likely to capture the symptoms being studied, and the timing of those measurements should correspond to the time frame in which effects are anticipated. On the basis of our review of the literature, there may be little role for routine HRQOL measurement in studies of drug therapy for metastatic disease, provided that comprehensive toxicity and symptom data are collected and that the drugs used have been sufficiently studied so that unexpected HRQOL effects are unlikely.

In contrast to the largely noncontributory effects of HRQOL outcomes on clinical decision making in trials involving biomedical interventions, trials of psychosocial interventions have often demonstrated measurable effects on HRQOL outcomes. These effects have most often been identified using detailed psychosocial questionnaires (e.g., POMS) rather than multidimensional HRQOL instruments (e.g., EORTC QLQ-C30 or FLIC). To the extent that specific dimensions of psychosocial functioning are targeted in these interventions, appropriate HRQOL or psychosocial instruments known to be responsive to change in those dimensions can be selected. Because the incorporation of such measures appears to be essential to identifying the beneficial effects of these interventions (or the lack thereof), psychosocial intervention trials will probably continue to use measures that are drawn from the field of psychology rather than from the HRQOL measurement arena. To some extent, psychosocial intervention trials have had more funding, staff, and expertise to collect HRQOL and psychosocial outcome data from individual patients than biomedical intervention trials, making detailed evaluation of psychosocial outcomes more feasible. In contrast, most HRQOL measurements in biomedical intervention trials have had limited funding, are time constrained because of the challenges of adding these measurements to clinical treatment and, therefore, have often used short assessment batteries (*see* Tables 3–6). Whether the HRQOL outcomes in biomedical intervention trials would have been more compelling with more detailed HRQOL measurements is an open question that is worthy of investigation.

In making decisions about the inclusion of HRQOL end points in clinical trials, increased trial complexity, respondent burden, and cost should be balanced against the expected gain in knowledge, particularly when toxicity and targeted symptom data are also being collected, so that resources for HRQOL measurement can be allocated to those trials in which benefits are likely to be greatest *(91,92)*. Our review provides little support for the routine incorporation of HRQOL measurements in all clinical trials in breast cancer when such measurement is intended to contribute to selection of optimal treatments. Although it is tempting to use other purposes of HRQOL measurement (e.g., description of patient experience and prognostic effects) as a justification for inclusion of these measurements in all randomized trials in breast cancer, the increased burden must be balanced against the likelihood that this information could be obtained using less expensive and time-consuming observational designs.

In terms of future research, there is a need for the development of targeted HRQOL instruments that contain items or scales that measure areas likely to be affected by breast cancer or its treatment that are not captured by general or even cancer-specific measures of HRQOL. Such items or scales include menopausal symptoms and cognitive functioning in trials of adjuvant therapy, and body-image symptoms (including arm symptoms related to surgery and radiation therapy) of long-term survivors in trials of primary therapy. This need could be addressed by the development of specific modules (an approach taken in the development of both the FACT and EORTC QLQ), by the addition of a small number of items (with appropriate validation) to existing questionnaires, or by the development of new questionnaires. It is noteworthy that treatment effects on social functioning were rarely identified in clinical trials using available HRQOL instruments. This lack of treatment effect may be because the treatments studied did not affect this domain; it may also be because this domain is poorly measured using available instruments. Existing instruments and any new instruments that are developed should be shown to be sensitive to clinically important changes in the domains they measure if they are to be used in clinical trials. This approach requires agreement by the research community, clinicians, and patients on what a clinically important change is (an area of active research) *(93)* and what scaling is sufficiently fine to detect those changes. It is also essential that sample size be calculated for HRQOL outcomes and not just for medical outcomes; these calculations should incorporate anticipated differences and variability in HRQOL outcomes.

Several general methodological and/or statistical issues that arise from the incorporation of HRQOL measurement into research of any type also need to be addressed. Examples of these issues include HRQOL instrument selection (which one? how many?); timing of HRQOL measurements (how often? over what period of time?); reconciliation of multiple HRQOL outcomes (i.e., convergence and divergence of results obtained from different HRQOL instruments or subscales at the same or different times); statistical analysis (multiple testing, use of summary statistics and measures, handling of missing data, and sample size calculations); and interpretation of results (medical outcomes versus HRQOL outcomes, hierarchy of HRQOL outcomes [e.g., are some symptoms or domains more important

than others in making treatment selections?], clinically meaningful differences). Much of this fundamental research is underway, and it should be undertaken alongside work on the development and validation of specific instruments.

Where do we go from here? It would probably be wise to wait for the maturation of a number of clinical treatment trials that include many of the high-quality HRQOL instruments that are currently available. Once these trials report their treatment and HRQOL results, we can probably come to firm conclusions about the added benefit of the inclusion of HRQOL assessments in treatment trials in breast cancer. Our findings in this review, however, suggest a need for caution in initiating new HRQOL studies in breast cancer using existing general or cancer-specific HRQOL instruments unless treatment equivalency is an expectation (especially in the adjuvant setting) or unless the quality-of-life question targets unique or specific questions that can only be assessed through patient self-report.

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NOTES

Editor's note: Dr. Black's work was supported in part by funds received from the National Cancer Institute in conjunction with the Cancer Outcomes Measurement Working Group.

We acknowledge the support provided by the Cancer Outcomes Measurement Working Group of the National Cancer Institute (U.S.) in the preparation of this manuscript. Dr. Ganz is a recipient of an American Cancer Society Clinical Research Professorship.

Manuscript received March 28, 2002; revised November 22, 2002; accepted January 9, 2003.