Review Article

A critical evaluation of quality of life in clinical trials of breast cancer patients treated with radiation therapy

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Abstract: The aim of this study was to investigate the extent to which health-related quality of life (HRQOL) parameters have been reported in phase III trials with breast cancer patients (BCPs) who received radiation therapy (RT). We also examine the frequency and correlates of significant HRQOL gains. A systematic review was conducted. When HRQOL was a study endpoint, we extracted data on the instruments used for HRQOL analysis, assessing if there was formal statistical comparison between study groups and the results of such comparisons as reported by the authors of the studies. In result, 182 trials were included. HRQOL was considered as endpoint in 38 (20.8%) of the studies and it was used as primary endpoint in 10.9% of them. Of 22 trials that had a positive primary endpoint, 18 had a significant benefit in HRQOL, in favor of the experimental arm. Of 13 trials that had a negative primary endpoint, there were no differences in HRQOL among the study groups. With respect to HRQOL assessment, statistical methods and definition of timing of evaluation were described in 32 (84.2%) and 36 (94.7%) trials, respectively. In conclusion, HRQOL has been infrequently investigated in trials in BCP who received RT. Statistical methods and timing of evaluation were infrequently described with sufficient detail to be informative.

Keywords: Quality of life (QOL); breast cancer; treatment; radiation therapy (RT)

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Introduction

Worldwide, breast cancer is the most common cancer and the main cause of cancer-related death in women (1). In the United States, breast cancer is associated with 230,000 new cases and 40,000 deaths per year (2).

Radiation therapy (RT) is an important and validated modality for the management of breast cancer patients (BCPs) in all clinical stages. In ductal carcinoma patients, post-operative RT nearly duplicates local control (LC) rates, for both invasive and *in situ* recurrence (3). For patients who underwent breast-conserving surgery, post-operative whole breast irradiation (with or without regional nodal irradiation) is comparable regarding local regional control and overall survival (OS) when compared to radical mastectomy (RM) alone (4-10). Moreover, after RM, post-operative RT is prescribed for patients with locally advanced breast tumor and high-risk factors such as lymph node involvement, tumor size >5 cm and/or positive surgical

margins (11).

Despite the improvements in RT techniques, the treatment toxicities can harmfully affect patients' quality of life (QOL) (12,13). In recent years, health care has progressively increased its interest in understanding health-related quality of life (HRQOL) as a crucial and meaningful endpoint, particularly in oncology (14). Usually, the primary objective of phase III randomized controlled clinical trial is to evaluate the effect of a selected intervention assessing clinical endpoints such as OS, disease-free survival (DFS) or progression-free survival (PFS), LC and treatment related toxicity (15). However, gradually more attention has been given to improving the patients' QOL throughout cancer treatment (16,17). Although HRQOL assessment is important for clinical practice (18), the role of HRQOL records in supporting RT as a therapy for BCPs has not been formally measured yet.

The aim of this study was to investigate the magnitude to which QOL parameters have been reported in phase III studies on BCPs who received RT as part of the oncologic treatment, as well as the frequency and correlates of significant QOL gains.

Methods

A systematic review was performed. We restricted the search to phase III randomized clinical trials (RCTs) of patients with breast cancer. Eligible trials needed to have RT intervention as a main element of treatment in at least one of the arms. The electronic search was conducted with no publication year, no language or publication status restrictions. We searched the MEDLINE (1966 to September 2015) database (*Table S1*). We also screened the reference lists of relevant studies to ensure we had the maximum number of possible trials identified

Selection of studies

Two independent reviewers (GN Marta and ET Leite) assessed and selected the appropriate articles and the reference lists from these sources were searched for additional trials. Trials identified by the search were evaluated to determine whether they met the inclusion criteria. A third reviewer (FY Moraes) resolved discrepancies where they occurred.

Collection of QOL data

For each phase III RCT identified, the general trial features of the study and data on the use of endpoints were extracted according to the standardized checklist, including HRQOL parameters. With regard to HRQOL as an endpoint in the studies, we first attempted to identify any mention in the paper of HRQOL data collection during the trial, or, when no such mention was found, the existence of a companion paper dedicated to HRQOL analysis separately. When HRQOL was a study endpoint, we extracted information from the paper on the instruments used for HRQOL analysis, assessing if there was formal statistical comparison between study arms and the results of such comparisons as reported by the authors of the studies. We considered HRQOL as a positive endpoint when at least one of all parameters assessed had statistical significance.

The minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials (19) was applied. This instrument involves 11 critical issues that a study should report to produce consistent HRQOL results. HRQOL study is considered high-quality reporting when a minimum of 8 of the 11 conditions are present.

Statistical analysis

Summary statistics were used to describe absolute number and frequency of HRQOL-related issues and phase III RCT characteristics.

Results

The initial search retrieved 2,224 references. After screening of the titles and abstracts of these references, 1,819 studies were excluded and 405 full-text articles were selected. Of these, 271 publications, corresponding to 182 trials, fulfilled the eligibility criteria and were the subject of this analysis. Two independent reviewers selected appropriated articles and on which levels of discrepancies between the reviewers were very low (the third reviewer needed to solve discrepancies in 3% of the cases only). The flowchart of the retrieved studies and the characteristics of the included studies are presented in *Figure 1* and *Table 1*, respectively. HRQOL was considered a formal endpoint in 38 (20.8%) of the included studies (20-32) and it was used as primary endpoint in only 10.9% of them. OS, DFS or PFS, LC, local regional control was the primary endpoint for 102 (55.8%) of the studies (33-44); toxicity was the primary endpoint for 44 (24.3%) of the 182 trials. Most trials—153 (84.0%)—focused on biomedical intervention (for primary management and adjuvant treatment) (45-57). The same

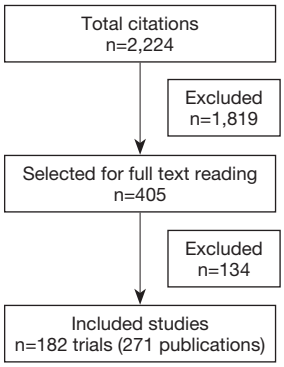

Figure 1 Flowchart of the process of study selection.

schedule of RT in all trial arms, with differences in other interventions, was the most common study.

Of 22 trials that had a positive primary endpoint, 18 reported significant benefit in HRQOL, in favor of the experimental arm. Of 13 trials that had a negative primary endpoint, there were no differences in HRQOL among the study groups (*Tables 2,3*). Statistical methods and definition of timing of evaluation were described for 32 and 36 trials with HRQOL assessment, respectively (*Table 2*).

Most HRQOL was assessed with tools common in HRQOL evaluation, with adequate psychometric properties; however, only 28% of the RCTs formally reported the tools' psychometric properties. The European Organisation for the Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30, with or without BR23) was the most frequently used tool in 17 (44.7%) of 38 studies. Eighteen trials (47.4%) used two or more HRQOL assessment tools. The Functional Assessment of Cancer Therapy (FACT-General or -Breast specific) with or without additional measures was used in 9 (23.6%) of 38 trials (*Tables 2,4*). Clinical significance and good quality data were shown in 51.4% and 48.6% of the RCTs with HRQOL as endpoint.

According to the minimum standard checklist for evaluating HRQOL outcomes, high-quality reporting was observed in 42.8% of trials. In *Table 5*, we summarize the results of 11 issues that comprise essential elements of this classification.

Table 1 Main characteristics of the 182 included randomized controlled trials of breast cancer and radiotherapy

Characteristics	N	%
Number of included patients		
≤100	42	23.0
>100 to <500	74	40.7
≥500 to <1,000	36	19.8
≥1,000	30	16.5
Interventions arms		
Same radiation therapy in all study arms, with differences in other interventions	93	51.0
Different radiation therapy in study arms	42	23.0
Groups differed by more than one intervention	47	26.0
Intervention group*		
Biomedical intervention	153	84.0
Non-biomedical intervention	29	16.0
Primary endpoint		
Overall survival	33	18.1
Disease-free or progression-free survival	26	14.2
Local control	38	20.8
Local regional control	5	2.7
Toxicity	44	24.3
Quality of life	19	10.5
Other	17	9.4
Quality of life as end point+		
Yes	38	20.8
No	144	79.2

*, type of intervention—articles were grouped based on to the category of intervention: biomedical intervention (for neoadjuvant, radical, adjuvant or palliative treatment) or nonbiomedical intervention (psychosocial intervention during the treatment); +, if the quality of life was formally considering as trial end point. N, number of trials; %, percentage.

Discussion

To the best of our knowledge, this is the first study to analyze the magnitude to which HRQOL parameters have been reported in phase III clinical trials in patients with breast cancer who underwent RT. Other authors previously assessed HRQOL issues in RCTs involving BCPs (58-61); however, the RT intervention was not necessarily performed and/or was not the focus on the articles.

After a confirmed diagnosis of breast cancer, the majority of patients underwent multimodality treatment (which includes surgery, RT and or systemic therapy). RT can

Table 2 Main characteristics of the 38 RCTs reporting QOL as an endpoint

Authors	Year^	Trial primary endpoint	Positive primary endpoint	Quality of life assessment*				
				QOL instruments	Statistical method was described#	Timing of QOL assessment was described	Statistically significant difference QOL+	QOL favors experimental arm+
Bazire *et al.*	2015	Toxicity	No	DLQI	No	Yes	No	No
Kirova *et al.*	2011	Toxicity	No	EORTC (QLQ-C30)	Yes	Yes	No	No
Whelan *et al.*	2015	Overall survival	No	EORTC (QLQ-C30)	–	–	–	–
Siekkinen *et al.*	2015	QOL	Yes	FACT-B	Yes	Yes	Yes	Yes
Williams *et al.*	2007	QOL	No	EORTC (QLQ-C30)	Yes	Yes	No	No
Hindley *et al.*	2014	Toxicity	Yes	DLQI	Yes	Yes	Yes	Yes
Lewis *et al.*	2014	Toxicity	Yes	EORTC (QLQ-C30)	Yes	Yes	No	No
Steindorf *et al.*	2013	QOL	Yes	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	Yes	Yes
Donker *et al.*	2014	Local regional control	Yes	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	No	No
Chandwani *et al.*	2014	QOL	Yes	MOS SF-36; RSCL	Yes	Yes	Yes	Yes
FitzHenry *et al.*	2014	Toxicity	No	FACT-B	Yes	Yes	No	No
Olivotto *et al.*	2013	Local control	No	BCCQOLQ	No	Yes	–	–
Haviland *et al.*	2005	Local control	Yes	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	Yes	Yes
Henderson *et al.*	2013	QOL	Yes	FACT-B	Yes	Yes	Yes	Yes
Sharp *et al.*	2013	Toxicity	No	EORTC (QLQ-C30)	Yes	Yes	No	No
Hau *et al.*	2012	QOL	Yes	EORTC (QLQ-C30)	Yes	Yes	Yes	Yes
Chen *et al.*	2013	QOL	Yes	FACT-G	Yes	Yes	Yes	Yes
Mutrie *et al.*	2012	QOL	Yes	FACT-G	No	Yes	Yes	Yes
Versmessen *et al.*	2012	QOL	Yes	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	Yes	Yes
Watson *et al.*	2012	Toxicity	No	FACIT-B	Yes	Yes	No	No
Hoffman *et al.*	2012	QOL	Yes	FACT-B; FACT-ES; POMS	Yes	Yes	Yes	Yes
Askoxylakis *et al.*	2011	Toxicity	Yes	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	–	–
Hoyer *et al.*	2011	QOL	No	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	No	No
Haines *et al.*	2010	QOL	Yes	EQ-5D / VAS; EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	Yes	Yes

Table 2 *(continued)*

Table 2 *(continued)*

Authors	Year^	Trial primary endpoint	Positive primary endpoint	Quality of life assessment*				
				QOL instruments	Statistical method was described#	Timing of QOL assessment was described	Statistically significant difference QOL+	QOL favors experimental arm+
Lundstedt *et al.*	2010	Toxicity	Yes	SSQ-DCCE	No	No	No	No
Vadiraja *et al.*	2009	QOL	Yes	EORTC (QLQ-C30); PANAS	Yes	Yes	Yes	Yes
Buijs *et al.*	2007	Overall survival	Yes	RSCL; MOS SF-36	Yes	Yes	Yes	Yes
Moadel *et al.*	2007	QOL	Yes	FACT-G; FACIT-F; FACIT-S	Yes	Yes	Yes	Yes
Titeca *et al.*	2007	QOL	Yes	FVDSQOFQ	Yes	Yes	Yes	Yes
Donovan *et al.*	2007	Overall survival	Yes	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	No	No
Mansel *et al.*	2006	Toxicity	Yes	FACT-B+4	Yes	Yes	Yes	Yes
International Breast Cancer Study Group	2006	QOL	No	IBCSG-QOL	Yes	Yes	No	No
Wells *et al.*	2004	Toxicity	No	DLQI	No	Yes	No	No
Gothard *et al.*	2004	Toxicity	No	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	No	No
Rayan *et al.*	2003	QOL	No	EORTC (QLQ-C30; QLQ-BR23)	Yes	Yes	No	No
Ganz *et al.*	2004	QOL	Yes	MOS SF-36; LLS; PANAS	Yes	Yes	Yes	Yes
Schmuth *et al.*	2002	Toxicity	No	MOS SF-36; Skindex	Yes	Yes	No	No
Wengstrom *et al.*	1999	QOL	No	CARES-sf	Yes	Yes	No	No

*, as assessed by authors themselves on the ground of their QOL and clinical outcome analysis; +, based on statistically significant results (at least P>0.5) reported in the studies; #, if was described a sample size calculation or statistical methods for QOL tools and/or outcomes; ^, if was considered the last publication related to the trial. QOL, quality of life; EORTC/QLQ-C30, European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire-C30; EORTC/QLQ-BR23, European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire-BR23; DLQI, Dermatology Life Quality Index; BCCQOLQ, Breast Cancer Chemotherapy Quality-of-Life Questionnaire; FACIT-B, Functional Assessment for Chronic Illness therapy's questionnaire for the breast population; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FACIT-S, Functional Assessment of Chronic Illness Therapy-Spiritual; FVDSQOFQ, French-Validated Dermatologic Specific Quality-Of-Life Questionnaire; POMS, Profile of Mood States; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Symptoms; EQ-5D/VAS, Generic Health-Related Quality Of Life Instrument With Visual Analogue Scale; CARES-sf, Cancer Rehabilitation Evaluation System; SSQ/DCCE, Study Specific Questionnaire—Division of Clinical Cancer Epidemiology; PANAS, Positive and Negative Affect Schedule; FACT-B+4, Functional Assessment of Cancer Therapy-Breast + 4 questionnaire; IBCSG-QOL, International Breast Cancer Study Group—Quality of Live form; LLS, Ladder of Life Scale; Skindex, Skin-specific index; MOS SF-36, Medical Outcome Study-Short Form-36; RSCL, Rotterdam Symptom Checklist.

Table 3 Comparison of primary endpoints of the studies and QOL significant results

Endpoint	Benefit in QOL (n)	No difference in QOL (n)	Total (n)
Primary endpoint positive*	18	4	22
Primary endpoint negative*	0	13	13

*, if the primary endpoint of the trial was positive or negative based on statistically significant results (at least P>0.5) reported in the studies. n, number of trials; QOL, quality of life.

Table 4 Quality of QOL measurements

Main QOL assessment tools	Number of trials	%
EORTC QLQ-C30 alone	6	15.7
EORTC QLQ-C30 plus QLQ-BR23	9	23.7
FACT-B alone	4	10.5
FACT-G alone	2	5.2
FACT-B plus additional measures	1	2.7
DLQI alone	3	7.9
Others	13	34.3
Studies using two or more QOL assessment tools	18	47.4

QOL, quality of life.

Table 5 Level of reporting according to the minimum standard checklist for evaluating QOL outcomes

HRQOL issue	Reports*	
	N	%
Conceptual		
A priori hypothesis stated[a]	23	65.7
Rationale for instrument reported[b]	24	68.6
Measurement		
Psychometric properties reported[c]	10	28.6
Cultural validity verified[d]	13	37.2
Adequacy of domains covered[e]	24	68.6
Methodology		
Instrument administration reported[f]	32	91.4
Baseline compliance reported[g]	29	82.9
Timing of assessments documented[h]	28	80.0
Missing data documented[i]	26	74.3
Interpretation		
Clinical significance addressed[j]	18	51.4
Presentation of results in general[l]	17	48.6

*, all numbers and percentages represent the positive answers regarding the related topic of the checklist; [a], if QOL end point and/or stated estimated changes due to the specific treatment were predefined; [b], if rationale for using a specific QOL measure were defined; [c], if previously validated measure was used or psychometric properties were described; [d], if the measure for the particular study population was validated; [e], if the main QOL measurements important for a generic cancer population and/or according to the specific research issue were assessed; [f], if who and/or in which clinical setting the QOL instrument was managed; [g], if the number of patients providing a QOL assessment before the beginning of treatment was informed; [h], if the HRQOL timing of assessment during the study was defined; [l], if the details on QOL missing data during the trial was mentioned; [j], if the QOL data being clinically significant from a patient's view and not only statistically significant; [l], if the QOL outcomes, giving any comments in regard of the results were performed for the authors. N, number of articles reporting item/number of articles to which item is applicable; QOL, quality of life.

cause acute and long-term adverse effects (AEs); however, higher-grade toxicities are relatively infrequent due to improvements in RT planning and delivery methods. Long-term AE, such as pneumonitis, cardiotoxicity and radiation-induced second malignancy can happen even many years after RT with important repercussions for the patients HRQOL (62). Thus, the evaluation of HRQOL is recognized as an essential element of the modern clinical oncological agenda, and HRQOL endpoints have been increasingly adopted in RCTs (17).

Overall, we demonstrated that HRQOL endpoints were used in 20.8% of RCTs in BCPs who receive RT. In most of the RCTs in which HRQOL were endpoints, formal methods comparisons between groups were described, although significant differences between groups were observed in 18 of 38 trials.

Currently, many instruments that aim at exploring HRQOL particularly in patients with breast cancer are available. The application of validated HRQOL tools might enable better understanding of the side effects of breast cancer treatment and their true consequences for the patients. As presented in *Tables 2* and *4*, all included trials used a validated HRQOL instrument whereupon most widely used tools were EORTC (QLQ-C30 and QLQ-BR23) followed by FACT-B (*Table 4*). Similar findings

were demonstrated by other authors (58). These results propose that EORTC (QLQ-C30 and QLQ-BR23) and FACT-B instruments are considered by investigators to be the standard assessment for the breast cancer trials setting, although there was no specific justification for the HRQOL instrument selection. This trend poses significant consequences, since the selection of HRQOL tools should encompass at least 3 fundamental elements (reporting, analysis and interpretation) of HRQOL data research. Formal explanation was not present in almost all RCTs, and its absence was often associated with the lack of a predefined HRQOL hypothesis.

Despite our study being a combined evaluation of all HRQOL instruments, a formal assessment of the tools used or HRQOL elements reported was performed (*Table 5*). This is a robust evaluation of HRQOL results in breast cancer that can potentially offer critical data regarding reporting, analyzing and interpreting of HRQOL literature.

It is important to recognize that we did not apply CONSORT-PRO (63) to evaluate the included RCTs in this study. CONSORT-PRO is a recent development that took the checklist and others into account. If we applied the CONSORT-PRO to the present data, we would be assessing studies on criteria that were not formally recommended until 2013. In this context, one of the limitations of our study is that we did not review the quality of the included RCTs. In fact, we reviewed the quality of the publications and in doing so understood that space limitations in journals may have meant that the authors were not able to report things in as much detail as they may have wished. Some other limitations are that we have not reviewed if HRQOL assessment was expected in the RCT's published protocol, nor if the applied HRQOL instrument had a proven validity for the specific population of each RCT. However, our study permits a comprehensive overview of HRQOL research in BCPs who receive RT as part of their treatment. This is an important issue that was also demonstrated for other authors in different scenarios such as locally advanced/metastatic breast cancer and melanoma.

In conclusion, our analysis shows that HRQOL has been infrequently investigated in RCT in BCPs who received RT. Statistical methods and timing of evaluation were frequently described with enough detail to be informative and applicable. However, significant benefit in HRQOL was frequently reported when a positive primary outcome was reported, showing that QOL can be an important predictor of better treatment outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Search strategy used for MEDLINE

Database	Search strategy
Medline (via PubMed), 09/29/2015	("Breast Neoplasms"[Mesh] OR Breast Neoplasm OR Neoplasm, Breast OR Neoplasms, Breast OR Tumors, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Breast Cancer OR Cancer, Breast OR Cancer of Breast OR Mammary Cancer OR Malignant Neoplasm of Breast OR Malignant Tumor of Breast OR Breast Carcinoma OR Cancer of the Breast) AND ("Radiotherapy"[Mesh] OR Radiotherapies OR Radiotherapy, Targeted OR Radiotherapies, Targeted OR Targeted Radiotherapies OR Targeted Radiotherapy) AND (Clinical Trial[ptyp])