Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials

Irina Ghislain, Efstathios Zikos, Corneel Coens, Chantal Quinten, Vasiliki Balta, Konstantinos Tryfonidis, Martine Piccart, Dimitrios Zardavas, Eva Nagele, Vesna Bjelic-Radisic, Fatima Cardoso, Mirjam A G Sprangers, Galina Velikova, Andrew Bottomley*, on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group, the Breast Cancer Group, and EORTC Headquarters*

Breast cancer is the leading cause of cancer death among women worldwide, and increasingly, randomised controlled trials of this disease are measuring the health-related quality of life of these patients. In this systematic Review, we assess the adequacy of methods used to report health-related quality of life (HRQOL) from 49 eligible randomised controlled trials of advanced breast cancer. We compare our findings with those from the literature to investigate whether the standard of HRQOL reporting in this field has changed. We conclude that the overall reporting of HRQOL has improved, but some crucial aspects remain problematic, such as the absence of HRQOL research hypotheses and the overemphasis on statistical rather than clinical significance. Additionally, new challenges are arising with the emergence of novel treatments and the advent of personalised medicine, and improved HRQOL tools are required to cover the range of side-effects of newer therapies.

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*Joint senior authors

European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium (I Ghislain MS, E Zikos MS, C Coens MS, K Tryfonidis MD, A Bottomley PhD)**; European Centre for Disease Prevention and Control, Stockholm, Sweden** (C Quinten MS)**; Breast Reconstruction Quality of Life Group, University of Bristol, Bristol, UK** (V Balta MS)**; Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium** (Prof M Piccart PhD)**; Breast International Group, Brussels, Belgium** (D Zardavas MD)**; Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria** (E Nagele PhD, Prof V Bjelic-Radisic PhD)**; Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal** (F Cardoso MD)**; Academic Medical Center, Amsterdam, Netherlands** (Prof M A G Sprangers PhD)**; and Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK** (Prof G Velikova PhD)

Correspondence to:
Ms Irina Ghislain, Quality of Life Researcher, European Organisation for Research and Treatment of Cancer, 1200 Brussels, Belgium
irina.ghislain@eortc.be

Introduction

With 1·7 million new cases and 521 900 deaths annually, breast cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer death in women.[1] Breast cancer accounts for 25% of all cancer cases and 15% of all cancer deaths among women.[1] Even though hormonal therapy, chemotherapy, and targeted and improved surgical and radiotherapy techniques, are decreasing the risk of disease relapse in patients with early-stage breast cancer, approximately 30–40% of patients will develop metastatic disease. Advanced breast cancer refers to either distant dissemination of the disease (metastatic breast cancer) or locally advanced breast cancer cases, which include primary cancers with extensive nodal (fixed or bulky axillary or supraclavicular [or both] or internal mammary) or skin involvement that are not amenable to initial surgery or radiotherapy with curative intent, as well as inflammatory breast carcinomas.[2–4]

Patients diagnosed with advanced breast cancer face the double burden of having an illness associated with significant symptoms, and the knowledge that advanced breast cancer, although treatable, is ultimately incurable. Usually, new cancer therapies are initially tested for their effectiveness in these groups of patients, leading to additional adverse events, but also often achieve disease control and prolonged survival.[4,5] The success of modern chemotherapy, targeted therapy, and endocrine treatments means that an increasing number of patients with metastatic breast cancer receive several lines of treatment. However, because the cure for this disease remains elusive, the two chief goals for most patients are to prolong survival and to improve health-related quality of life (HRQOL).[6]

Consequently, HRQOL assessment in randomised controlled trials assessing new treatments for this population is invaluable. HRQOL questionnaires often cover physical symptoms and functioning domains, and provide a patient-reported assessment of their health and QOL in cancer clinical trials.[7]

The number of novel targeted and immunotherapy agents for many cancers, including advanced breast cancer, has had an unprecedented increase in the past 5 years.[8] These agents often differ from traditional treatments in their method of action and effectiveness, administration, and especially in their side-effects profile, raising challenges for oncologists both in terms of safe delivery and monitoring of toxicities, as well as in assessing the benefit–risk ratio for patients balancing between disease control and side-effects.[9,10] Some of the immune-modulated adverse events of the new therapies can be serious and life-threatening; although most are low grade, they are usually long-lasting (such as diarrhoea, skin rash, and stomatitis), and thus substantially affect patients' daily lives.

In this exciting but challenging time, robust methods should be adopted in clinical trials to appropriately assess patient symptoms, side-effects, functioning, and HRQOL, alongside the traditional clinical outcomes of progression-free and overall survival. Furthermore, new tools should be developed to ensure an objective investigation of the additional benefit provided by new drugs, such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS),[11] which includes HRQOL that increases or decreases the score of each new treatment studied. This type of tool should be widely used, because it would help decision makers to prioritise access to expensive new therapies.

We undertook this systematic literature Review as a continuation of the review by Bottomley and Therasse[12] with the aim of assessing HRQOL methods as incorporated in therapeutic advanced breast cancer randomised controlled trials (RCTs) since 2001. Key recommendations of the previous review were: the necessity of a clear

hypothesis and the underlying research questions of the HRQOL assessment; the use of valid and disease-specific HRQOL measures; the importance of a high compliance level to reach conclusions on a longitudinal basis; the need for a good statistical analysis plan that addresses missing data to avoid bias; and discussion of clinical significance to help to interpret the results in a meaningful way. Additionally, more guidelines, including several reports and reviews[7,13–15] have been published regarding the reporting of HRQOL results,[16,17] highlighting that the added value of HRQOL assessment was highly dependent on the rigour of its methods and reporting, and recommending improvements in the methods of assessing HRQOL. Our systematic Review assesses data obtained from RCTs of advanced breast cancer published between 2001 and 2014, compares findings with those from a previous review,[12] and investigates how the research community for advanced breast cancer has integrated the recommendations and decisive importance of HRQOL-assessment methods.

Methods

Search strategy and selection criteria

We did a systematic literature search on Nov 1, 2014, (figure 1) using the methods described by Bottomley and Therasse[12] and the guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions.[18] Our inclusion criteria were: published RCTs of adult female patients (aged 18 years or older) with advanced breast cancer receiving anticancer treatments (chemotherapy, targeted therapy, or endocrine therapy), with sample sizes of at least 50 patients. Studies had to be published in English between January, 2001, and November, 2014, regardless of starting or completion date, and had to report the clinical results of the RCT (ie, no methodological or review publications). We allowed the inclusion of companion papers that focused only on HRQOL, and reviewed these in conjunction with the original publication. RCTs had to include patient-reported HRQOL endpoints (not reported by a third party) and had to be published in a peer-reviewed journal. RCTs that assessed only psychological, supportive, or supplementary interventions (defined as any other interventions that did not include anticancer therapy) were excluded.

We identified relevant references published from Jan 1, 2001, to Nov 1, 2014, through PubMed using the following search strategy: (quality of life[MeSH Terms] OR quality of life[Text Word]) AND (advanced[All Fields] OR metastatic[All Fields]) AND breast cancer[Text Word] AND (Randomised Controlled Trial) AND (breast neoplasm[MeSH Terms]) AND (Clinical Trial[ptyp] AND ("2001/01/01"[PDat]: "2014/11/01"[PDat]) AND Humans[Mesh]). We also did a manual search of the literature and checked references of publications to find relevant references for inclusion.

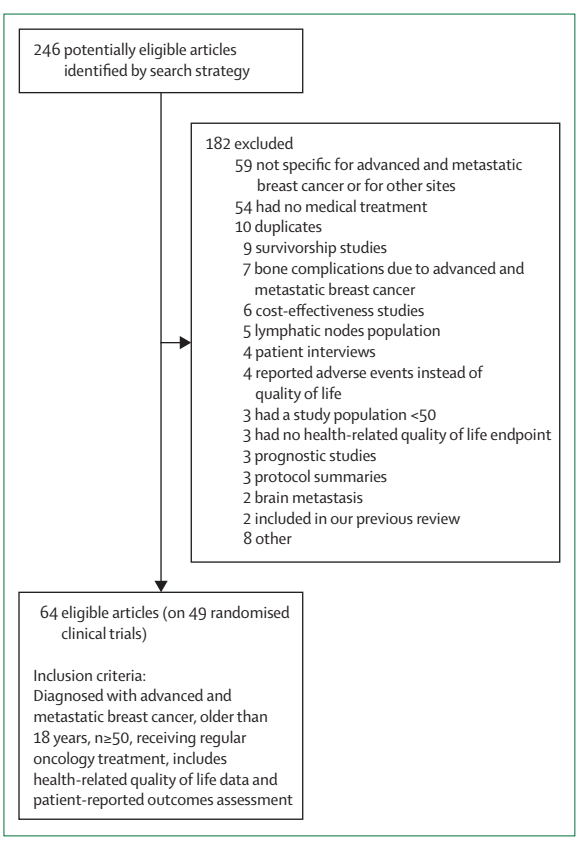

Figure 1: **Search strategy flowchart for the inclusion and exclusion of studies**
HRQOL=health-related quality of life.

Data extraction and analysis

The publication type was restricted by article type (ie, clinical trial, review, etc) taking into account all clinical trials irrespective of type and phase. We used no restrictions in the search field description. We assessed all identified studies using a published and established checklist of assessment criteria.[16] Two teams of reviewers (IG and CQ, and EZ and VB) assessed half the publications each with the same main criteria as used in our previous systematic literature reviews[19,20] that were classified into four categories: first, key characteristics of the RCTs; second, trial design aspects relevant to HRQOL endpoints; third, the quality of the HRQOL measurements; and fourth, statistical analysis and presentation of HRQOL results. A fifth reviewer (CC) was available as a mediator to solve disagreements in a consensus-based reconciliation. The reviewers then compared the results (absolute numbers and percentages) with those from the Bottomley and Therasse review[12] in a descriptive manner to identify notable changes. Because AB and CC are co-authors in two articles included in this Review,[21,22] they were excluded from the selection process of the literature search. MP was also excluded from reviewing the four articles where she was co-author.[22–25]