Article:
Ghislain, I, Zikos, E, Coens, C et al. (11 more authors) (2016) Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials. The Lancet Oncology, 17 (7). e294-e304. ISSN 1470-2045

https://doi.org/10.1016/s1470-2045(16)30099-7

Health-Related Quality of Life in Locally Advanced and Metastatic Breast Cancer: A Systematic Review on Reporting of Methodological and Clinical Issues in Randomized Controlled Trials of Anti-Cancer Treatments

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Keywords

Health-Related Quality of Life, Advanced Breast Cancer, Literature Review, Randomized Controlled Trials, EORTC

List of Abbreviations

ABC	Advanced Breast Cancer
DDC	Daily Diary Cards
EQ-5D	EuroQOL Five Dimension Scale
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Core Quality of Life Questionnaire
EORTC QLQ-BR23	EORTC Breast Cancer Module
FACT-B	Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer
HADS	Hospital Anxiety Depression Scale
HRQOL	Health-Related Quality Of Life
LABC	Locally Advanced Breast Cancer
MBC	Metastatic Breast Cancer
QoL	Quality of Life
OS	Overall Survival
POMS	Profile of Mood Scale
PFS	Progression-Free Survival
PRO	Patient-Reported Outcomes
RCTs	Randomized Controlled Trials
RSCL	Rotterdam Symptom Checklist
TTP	Time to Progression
VAS	Visual Analogue Scale

Abstract

Breast cancer is the leading cause of cancer death among females worldwide; increasingly, randomized controlled trials of this disease measure the health-related quality of life of patients. In this Systematic Review we assess the adequacy of reporting of health-related quality-of-life (HRQOL) methods in 49 eligible randomized controlled trials of advanced breast cancer. We compare our findings with those from the previous review to investigate whether the standard of HRQOL reporting in this field has changed. We conclude that the overall reporting of HRQOL has much improved since the last review, but certain crucial aspects remain problematic such as the absence of the HRQOL research hypotheses and the overemphasis on statistical rather than clinical significance. In addition, new challenges are arising with the emergence of novel treatments and advent of personalized medicine and newer tools are required to cover the range of side effects of newer therapies

Funding

Financial support for this research was provided by the EORTC Cancer Research Fund.

Introduction

With 1.7 million new cases and 521,900 deaths annually, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide. Breast cancer accounts for 25% of all cancer cases and 15% of all cancer deaths among females[1].

Even though hormonal therapy, chemotherapy, 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 (ABC) refers to either distant dissemination of the disease (metastatic breast cancer-MBC) or Locally advanced Breast cancer (LABC) cases which include primary cancers with extensive nodal (fixed or very bulky axillary and/or supraclavicular or internal mammary) and/or skin involvement, not amenable to initial surgery or radiotherapy with curative intent, as well as inflammatory breast carcinomas[2–4].

Patients diagnosed with ABC face the double burden of an illness associated with significant symptoms and the knowledge that ABC, although treatable, is ultimately incurable. New cancer therapies are usually initially tested for their effectiveness in this group of patients, leading to additional adverse events, but also often achieving disease control and prolonging survival with metastatic disease[4,5]. The success of modern chemotherapy, targeted therapy and endocrine treatments means that an increasing number of patients with metastatic breast cancer receive multiple lines of treatments. However, as the cure for this disease remains elusive, for most patients prolonging their survival and improving their Health-Related Quality of Life (HRQOL) are two chief goals which reflect benefit from treatment[6].

Consequently, HRQOL assessment in Randomized Controlled trials (RCTs) evaluating new treatments for this population is invaluable. HRQOL questionnaires cover physical symptoms and functioning domains, and provide a patient-reported evaluation of their health and QoL in cancer clinical trials[7]. The assessment of HRQOL is made through the use of standardized and validated patient self-assessment tools.

This systematic literature review was undertaken with the aim of evaluating HRQOL methodology reporting as incorporated in therapeutic ABC RCTs since 2001 and is conducted as

a continuation of the review by Bottomley and Therasse published in 2002[8]. 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 specific disease HRQOL measures; the importance of a high compliance level in order to reach conclusions on a longitudinal basis; the need for a good statistical analysis plan which addresses missing data to avoid bias and discussion of clinical significance to help interpretation of the results in a meaningful way. In addition, more guidelines, including numerous reports or reviews[7,9–11] were published regarding the reporting of HRQOL results[12,13], highlighting that the added value of HRQOL assessment was highly dependent on the rigor of its methodology and its reporting and improvements of HRQOL methodology were recommended.

Currently, we are witnessing an unprecedented increase in the number of novel targeted and immunotherapy agents in many cancers, including advanced breast cancer[17]. These agents often differ from the traditional treatments in their mode of action and effectiveness, administration, and particularly side effects profile, raising challenges for oncologists both in terms of safe delivery and monitoring of toxicities, and assessing the cost-benefit for patients balancing between disease control and side effects[18,19]. Some of the immune-modulated adverse events of the new therapies can be serious and life-threatening, but the majority is relatively low grade, usually long lasting (such as diarrhea, skin rash and stomatitis), thus impacting significantly on patients' daily lives. In this exciting but challenging time, it is essential to adopt robust methodology in clinical trials to appropriately evaluate patient symptoms, side effects, functioning and HRQOL, alongside traditional clinical outcomes of progression-free and overall survival.

Furthermore, new tools developed to ensure an objective evaluation of the additional benefit provided by new drugs, such as the ESMO Magnitude of Clinical Benefit Scale[20], have HRQOL as a key factor of this evaluation that increases or decreases the score of each new treatment evaluated. This type of tool will become widely used, helping decision-makers to prioritize access to expensive new therapies.

This systematic review evaluates data collected from RCTs on ABC published in a 13-year span, compares findings with those from the previous publication and evaluates how the ABC research

community has integrated the recommendations and decisive importance of HRQOL methodology.

Methods

In this systematic literature review, the methodology described by Bottomley and Therasse and the guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions[21] were implemented.

The inclusion criteria for the RCTs were: adult patients (18 years or older) with ABC receiving anti-cancer treatments (chemotherapy, targeted therapy, 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 (i.e. no methodological or review publications). Companion papers focusing only on HRQOL were included, and were reviewed in conjunction with the original publication. The RCTs had to include patient-reported HRQOL endpoints and be published in a peer-reviewed journal.

Exclusion criteria were any RCTs which evaluated psychological, supportive or supplementary interventions. Supplementary treatments were defined as any other interventions that did not include anti-cancer therapy.

Search strategy and selection criteria

References for this review were identified 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 (Randomized Controlled Trial) AND (breast neoplasm[MeSH Terms]) AND (Clinical Trial[ptyp] AND ("2001/01/01"[PDat] : "2014/11/01"[PDat]) AND Humans[Mesh]). Hand searches and checking of references of publications was also undertaken.

The publication type was restricted to the subheading of clinical trial, taking into account all clinical trials irrespective of type and phase. No restriction in the search field description was performed. All identified studies were evaluated, using a published and established checklist of evaluation criteria[12]. Two teams of reviewers (IG-CQ and EZ-VB) assessed half the publications

on the same main 29 evaluation criteria as used in our previous systematic literature reviews[14,16] classified in four categories: (1) key characteristics of the RCTs; (2) trial design aspects relevant to HRQOL endpoints; (3) the quality of the HRQOL measurements; and (4) statistical analysis and presentation of HRQOL results. A fifth reviewer (CC) was available as a mediator in case of disagreement.

The results were then compared with the Bottomley and Therasse review[8] in a descriptive manner to identify notable changes between the two reviews.

Results

Identified RCTs

Our search identified 246 publications, with only 64 (26%) being eligible for inclusion, corresponding to 49 evaluable RCTs that reported HRQOL. One hundred and eighty-two manuscripts were excluded due to e.g., non-ABC specific criteria, treatment type, duplication, small sample size, and inclusion in the Bottomley and Therasse review, which covered part of year 2001 (Jassem 2001 and Buzdar 2001) (Figure 1).

The 49 identified ABC RCTs cover a 12-year span representing an increase of 29% compared to the previous Bottomley and Therasse review (19 trials over a six-year span), and involved a total number of 19,917 patients. The key criteria evaluated in this systematic review and the overall rating of the RTCs are summarized in Table 1 and the whole set of criteria are presented as supplementary online files (Appendices 1–4).

For 14 out of 49 (29%) RCTs, the HRQOL data were published in a companion paper. One additional paper was published on missing data, amounting to 64 articles included in our review. No RCTs were identified in 2014.

We also included two papers[22,23] meeting the inclusion criteria but that did not present HRQOL data. The authors stated that they planned to do it in a separate article. This was not yet the case at the time we reviewed the selected trials. HRQOL criteria were then listed as Not Applicable (NA), and for that reason our percentages of HRQOL criteria are calculated excluding these two studies (X/47 or X/48 instead of x/49).

INSERT FIGURE 1

Key characteristics

Thirty-five out of 64 articles (55%) were published in high impact factor (>10) peer-reviewed clinical journals. Concerning the 14 HRQOL companion papers, six were published in the year following the publication of the main clinical results, six others within two years, and two papers were published more than two years later. Thirty-eight out of 49 RCTs (78%) were industry-sponsored or affiliated with the pharmaceutical industry through one or more of the authors/investigators as noted in the financial sponsorship part of the articles. Ninety-one percent of international trials are industry funded, compared to 53% of the single-country ones. Five trials had HRQOL as primary endpoint and only one of them was industry-supported (online appendix 1).

INSERT TABLE 1Main clinical characteristics (table 2)

Overall survival (OS), progression-free survival (PFS) or time to progression (TTP) was the primary endpoint for 44 trials (90%) and HRQOL was the primary endpoint for 5 trials (10%). The majority of RCTs focused on chemotherapy alone (57%), on chemotherapy in combination with targeted agent (27%) or hormonal therapy alone (10%).
Out of the 44 trials with OS/PFS/TTP as primary endpoint, 24 (55%) reported significant differences in a clinical endpoint between the treatment arms (10 chemotherapy alone, 2 hormonal therapy alone, 10 chemo+target agent, 1 chemo+hormonal therapy and 1 hormonal+target agent). Additionally 12 trials (9 assessing chemotherapy and 3 hormonal therapy) without significant difference in OS/PFS/TTP concluded that the experimental treatment was at least as good as the standard treatment, although only 3 were non-inferiority trials. The remaining eight trials concluded that the standard treatment was better than the experimental, despite insignificant differences.

INSERT TABLE 2

Main HRQOL results (Tables 2 and 3)

A significant difference in HRQOL, next to a positive clinical outcome, was reported in 8 (33%) out of the 24 trials, 6 of them favoring the experimental arm. (Four were chemo + target therapy trials and two were chemo trials.) Two trials with benefit in terms of OS/PFS but harm in terms of HRQOL were chemo trials. One[37] was high dose versus standard dose chemo with significant difference in PFS but overall deterioration in HRQOL for the experimental arm. The other[25] was a combination of two chemo agents versus one alone, with better OS and PFS and more pain in the experimental arm. Of the remaining 22 trials without clinical benefit, a better HRQOL in favor of the experimental arm was reported in 4 trials (18%) (3 out of 4 RCTs had a primary HRQOL endpoint) and 1 trial showed a HRQOL deterioration in the experimental arm.

INSERT TABLE 3

Trial design aspects relevant to HRQOL endpoints

The method of randomization, HRQOL hypothesis and patient selection criteria are accessible in online Appendix 2. For 10 of 48 (21%) trials, an a priori hypothesis on the expected overall HRQOL outcome was provided in the introduction or statistical analysis sections. These hypotheses described the anticipated differences in HRQOL between treatment arms. Baseline HRQOL assessment was mandatory for study participation in 5 out of 47 (11%) of the RCTs. Sample sizes of the RCTs varied from 66 patients to 1,300 patients. The five out of 49 RCTs (10%), with HRQOL as primary endpoint, all focused on chemotherapy alone.

Quality of the HRQOL measurements

The measurement of HRQOL was carried out using tools common in HRQOL assessment, with acceptable psychometric properties (online Appendix 3). The core EORTC Quality of Life Questionnaire (EORTC QLQ-C30) was the most frequently used tool in 22 of 48 RCTs (46%).

In 10 of those 22 studies EORTC QLQ-C30 was supplemented with the EORTC Quality of Life 23-item Breast Cancer-specific Questionnaire (EORTC QLQ-BR23). The Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer (FACT-B) was used in 19 out of 48 trials (40%), the Rotterdam Symptom Checklist (RSCL) was used in 4 of the studies (8%) and the EuroQOL Five Dimension Scale (EQ-5D) was used in two (4%). In the single country trials, North American countries are systematically using the FACT-B questionnaire whilst European countries are using the EORTC QLQ-C30, except for one UK trial using the FACT-B. International studies equally use EORTC QLQ-C30 (11 trials) and FACT-B (11 trials).

The validity and reliability of the instruments used were reported by referencing the appropriate validation studies in 37 out of 48 RCTs (77%). In the remaining 11 RCTs, no statement or reference was provided with regard to validity or reliability, although most of the selected instruments did have sufficient psychometric properties.

In 9 studies out of 48 (19%) the cultural validation process of the instrument was not applicable, as it was used in a population already covered by the original development, mainly English language. The cultural validity of the instrument used was reported in only 10 of the remaining 39 trials (26%), which stated they used a translated version of a HRQOL tool in a population for which the tool was not originally developed, and 29 of 39 (74%) studies did not report on the cultural validation process or study, regardless of whether or not the instrument was culturally validated.

The HRQOL domains covered by the questionnaires were considered adequate in most of the RCTs (69%), since both symptoms and functional scales were captured in 33 out of 48 RCTs. However, most studies (79%) did not specify a research hypothesis, complicating the evaluation of the appropriateness of the domains.

Rationale for selecting the HRQOL instruments was presented in 10 of the 47 studies (21%). It was defined that a rationale is presented if the authors clearly referred to the characteristics of the HRQOL instrument used, or if they specified the reasons for choosing the particular HRQOL instrument.

Details on the administration procedure were not commonly reported. Eight RCTs out of 47 (17%) noted some details, e.g. the exact place or time of questionnaire completion. All but two RCTs reported the timing of HRQOL assessments while baseline compliance was reported in 31 of the 47 studies (66%).

INSERT TABLE 4

Statistical analysis and presentation of HRQOL results

In 42 of 47 RCTs (89%) statistical tests for between-treatment HRQOL differences were specified (online Appendix 4). In six studies the exact test for significance was not clearly explained, or was planned to be addressed in a future publication. Out of 42 RCTs in which a test of statistical significance was reported, 26 RCTs (62%) demonstrated at least one significant difference at any time point ($p < 0.05$) in HRQOL scores. The clinical meaningfulness of HRQOL differences was reported in 23 of the 47 RCTs (49%). The presentation of HRQOL results was considered adequate when reporting of domains was consistent with the intended analysis reported in the introduction or methods section, which was the case in 22 of the 49 RCTs (45%). Twenty-four of the 49 RCTs (49%) were considered limited when only HRQOL details were reported without giving the full range of scores, without using graphs or tables or without discussing the meaning or implications of HRQOL results. Details on missing data were discussed in 18 of 47 (38%) of the trials, while 13 out of 47 (28%) reported limited or descriptive information on missing data. In the 16 remaining RCTs (34%), no details on missing data were reported.

Applying alternative checklist for quality of HRQOL outcomes

In an attempt to sum up the evaluation of HRQOL assessment in ABC trials, we compared our results with the checklist developed by Efficace et al[12], which comprises 11 essential issues that a trial should address to generate reliable HRQOL outcomes (hypothesis stated, rationale for instrument reported, psychometric properties reported, cultural validity verified, adequacy of domains covered, instrument administration reported, baseline compliance reported, timing of

assessment documented, missing data documented, clinical significance addressed, presentation of results). According to the checklist, , the HRQOL data are judged as high-quality reporting if at least 8 of the 11 criteria were satisfied, of which 3 (baseline compliance reported, psychometric properties reported, missing data documented) have to be high priority concerns.

Applying these rules to the 47 selected trials, we found that 10 trials (21%) stand out due to their rigorous HRQOL methodology reporting. Nine of them published their HRQOL reports in a companion paper and the tenth had HRQOL as primary endpoint.

Moreover, 5 of the 8 trials with significant difference in HRQOL next to an improvement in clinical outcome form part of these 10 trials: 63% with significant difference in both outcomes have high-quality reporting.

Comparing the 2 periods (1995-2001/2002-2014) on the main recommendations made by Bottomley and Therasse in 2003

In comparison with the Bottomley and Therasse review, we see an increase of 44% in the use of a disease-specific measure, a 19% increase in the studies that provided information on missing data (detailed plus limited information), a 34% increase in the studies that reported clinical significance and an 18% increase in studies that provided detailed information on the assessment of HRQOL. Contrarily, a decrease of 11% was observed in the studies that did not provide a research hypothesis and a 10% decrease was seen in the studies where HRQOL was the primary endpoint. No difference was found in reporting of the applied tests of statistical significance.

INSERT FIGURE 2

Discussion

The aim of this systematic literature review was to evaluate the HRQOL methodology reporting in ABC RCTs since 2001. For this review we did not consider only studies with metastatic breast cancer patients but also studies that included patients with inoperable locally advanced disease, whose prognosis is often unfavorable and comparable to those with distant disseminated disease despite aggressive treatment and mainly studies that enrolled both patient groups[2–4].

Overall, we observed an increase of 29% in the number of ABC RCTs which involved an HRQOL measurement, when compared to the previous review covering RCTs between 1995 and 2001[8]. Our review found that the majority of the ABC studies with HRQOL assessment were international and supported by commercial sponsors who seem to play an important role in the inclusion of HRQOL assessment. The international studies appeared to be more reliant on industry support than national studies.

It is worth noting that it was sometimes difficult to evaluate whether or not a trial was industry-funded based on the published article. Authors are required to provide full financial disclosure when reporting results to increase transparency. However, the compulsory nature makes it difficult to distinguish relevant conflict of interest from bona fide support.

The patient-informed consent procedure and the eligibility criteria are mandatory components of RCTs and now commonly reported. However, nearly half of the RCTs did not report the method of randomization. This induces a potential imbalance which could affect HRQOL comparisons (e.g., differences in reporting of HRQOL issues can be due to gender, age, stage of disease, etc, and these need to be clearly defined). Most HRQOL outcomes are defined as secondary rather than primary endpoints, which is striking at this late – and thus lethal – stage of the disease. Furthermore, HRQOL baseline assessment was rarely mandatory which generally leads to limited compliance and thus affects the validity of the results.

Compared to the previous review by Bottomley and Therasse[8], we see major improvements in the quality of reporting. This has increased for several high-priority criteria, such as the appropriateness of the measure and the use of disease-specific measures. A way to reinforce this improvement would be to supplement these measures by treatment specific items based on the

nature of therapy tested. This can among other things be done via the EORTC item bank[71]. Progress has been made in the reporting of missing data: almost two thirds of the ABC RCTs provided information on missing data (detailed plus limited information). The reporting of missing data was a main recommendation of the Bottomley and Therasse review, where less than half of the trials addressed it[8] (Figure 2)**.** Even though this figure is encouraging when compared to the previous review, the reporting of missing data by treatment arm and over time needs to be standardized to aid the interpretation of HRQOL results. Also the reporting of clinical significance in addition to statistical significance has much improved. This progress reflects three of the five major recommendations addressed by Bottomley and Therasse in the previous review and is therefore encouraging. It allows robust and reliable HRQOL data in RCTs, which in turn will improve clinical decision making. Clinical significance in particular should inform decision making process as it relates to the qualitative magnitude of the observed treatment effect. Statistical significance on the other hand indicates the reliability of the results and depends on sample size calculations.. When clinical and survival outcomes between treatments become smaller, positive HRQOL outcomes derived from a rigorous HRQOL methodology will primarily/predominantly influence the treatment decisions[10,12].

The most important aspect in HRQOL methodology which needs to be better reported is the a priori hypothesis of the HRQOL assessment. This aspect was less well reported over time: where only 32% of the studies reviewed by Bottomley and Therasse drew attention to a hypothesis, only 21% of our studies did. This is also a key recommendation of the literature in this field. As already mentioned[8,12] , defining and reporting a hypothesis is an essential requirement of good study design. The design of HRQOL components depend on the objective. A clear objective and specific hypotheses improves the credibility of the results, and when the hypothesis is directed at single or small numbers of outcomes, multiple testing of HRQOL variables is reduced. A clear definition of the treatment success or failure regarding HRQOL is especially critical when the treatment arms under investigation have different emergent toxicity profiles,

The lack of a clear objective and hypotheses in many RCTs might, in part, be due to the increased use of targeted therapies. In the first half of the period covered by our review, a fifth of treatment strategies evaluated new targeted agents combined with chemotherapy while in the second half, it reached nearly 50% (none in the previous review). In this new field it is difficult

to formulate hypotheses and to justify the choice of an instrument. Indeed, only 13% (2/15) of targeted therapy trials reported a hypothesis where 29% (8/28) of chemotherapy trials did.

We note that for approximately a third of the trials, the HRQOL results were detailed in a companion paper, but likely in journals with a less wide clinical audience and lower impact factor. Including the HRQOL results in the primary publication can be a limiting factor because of the space restriction, but has the advantage of providing up-to-date outcomes. Companion papers on HRQOL of good quality reporting thanks to their methodological rigor were sometimes published more than two years after the clinical outcomes, limiting their added values to the medical decision process and to patients themselves (six papers were published in the year following the main publication, six within two years). But this problem is expected to be mitigated with new EU regulations of June 2014 that require all endpoints to be published within a limited time from the end of a trial[72]. Nevertheless, it is promising to see that the number of additional HRQOL papers has more than doubled in the second phase of our review (four between 2001 and 2007 and nine between 2008 and 2013) indicating a growing interest for a specific part of the research community in ABC RCTs.

For studies that assess HRQOL across various cultures, investigators should choose only measures that have proven validity in a given cultural group. This may not be a straightforward task in a large international setting with many languages/cultures involved or when using an old questionnaire with outdated references or support. However, verification of the source questionnaire material should take place during the design of the study when the protocol is written and CRFs created. At the time of publication, cultural validity can be simply extracted from the study protocol if the trial was well documented and managed. Overall, the validity and reliability of the tools used as well as their cultural validity were adequately described. That can be explained by today's availability of well-validated standard HRQOL tools. Indeed, the most widely used tool was the EORTC QLQ-C30, which includes many of the characteristics defined by the Guidance for Industry as being necessary for an effective HRQOL patient-reported assessment tool (e.g. adequacy of validity and reliability), followed closely by the FACT-B. This suggests that they are considered by researchers to be standard tools for use in ABC RCTs, and consequently they are used without providing a rationale for the choice. This shortcut has significant implications because the choice of instrument impacts the reporting, analysis and

interpretation of the HRQOL outcomes, and therefore deserves adequate justification. Such justification was found lacking in many of the reviewed trials, and its absence seems to become intimately linked in a vicious circle with an absence of a hypothesis.

Furthermore, it must be noted that we have already entered the era of personalized cancer medicine[73]. An increasing number of molecularly targeted agents is being added to our therapeutic armamentarium, with some of them exerting high antitumor activity for patients with tumors that bear specific molecular aberrations[17]. These drugs have different toxicity profiles compared to the conventional therapeutic agents used[74] so far and they are associated with increasing financial burden in cancer care[18]. Thus, it becomes even more relevant to have a rigorous assessment of the impact of these new drugs on the HRQOL of patients receiving them, so that better-informed clinical decisions can be made by oncologists. It must be noted that guidance from regulatory authorities concerning the efficient incorporation of HRQOL-related endpoints in RCTs can further advance the field[75]. Last, there have been recent efforts to standardize the magnitude that can be expected from anti-cancer therapies, as exemplified by the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS[19]). This scale takes into account HRQOL-related performance of anticancer drugs, along with clinical outcome and toxicity-related results, thus representing a more holistic approach to new drug evaluation. Further guidelines are needed to improve such aspects as design, conduct, data collection, analysis and reporting of HRQOL data from RCTs. This is not limited to breast cancer field only but all oncology domains. Specific recommendations fall beyond the scope of our paper but several key initiatives, such as the Setting International Standards of Analyses of Quality Of Life in cancer clinical trials (SISAQOL) are expected to help remedy this problem (http://groups.eortc.be/qol/sisaqol-project).

We note also that the currently available instruments in ABC are not well attuned to detect plausible differences between newer competing therapies, regarding their differential impact on [76,77]. Targeted therapies are initially tested in patients with metastatic cancer, but the range of their side effects is not covered by the two main tools, the EORTC-BR23 and the FACT-B, developed many years ago. There is an increasing need for an up-to-date questionnaire dedicated to ABC patients. Specific tools designed to evaluate new types of side effects seen with some of the new drugs are needed. Especially with the latest developments, the next area of interest will

be to evaluate HRQOL in trials with immunotherapeutic drugs. New tools tailored to ABC patients would improve the quality of HRQOL evaluation and make it more meaningful for clinical practice.

Our literature review has several limitations. This review can only evaluate results which have been published and is therefore subject to publication bias. Not only are unpublished RCTs excluded, also RCTs which included HRQOL evaluation by design but did not publish such results would not be identified by our evaluation. Our review therefore gives a selected and potentially overoptimistic view of the true HRQOL reporting status. As mentioned, no RCTs were identified in 2014, probably due to a delay between the date a paper is published and the date the publication is entered in databases.

Finally, our research plan was limited to reviewing the published articles only. We did not review the protocols or the statistical analysis plans and therefore cannot assess whether certain shortcomings are due to study design or due to reporting restrictions such as limited journal space.

Conclusion

While most of the experts' recommendations have been broadly followed by the research community during the past decade, a major recommendation that is still underreported is the specification of the HRQOL research hypothesis. With treatments becoming increasingly tailored to the patient, it is crucial to clarify the expectations of the HRQOL endpoint at the onset of a trial by making the hypothesis a standard requirement. Many aspects of implementation, conduct and interpretation hinge on a correct prior statement of the HRQOL objective. A better adherence to existing HRQOL reporting guidelines will lead to a more efficient understanding of HRQOL outcomes

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Authors' Disclosures of Potential Conflicts of Interest

Dr. Andrew Bottomley and Mr. Corneel Coens are co-authors in two (Bottomley et al 2004, Bottomley et al. 2005) of the articles used in this review. However, they were excluded from the entire review of the selected articles. Prof. Martine Piccart was also excluded from the review of the articles where she was co-author (Burris et al. 2003, Therasse et al. 2003, Biganzoli et al. 2003, Bottomley et al. 2004, Chia et al. 2008 and Baselga et al. 2012). The first of the authors indicated no potential conflict of interest. Dr. Andrew Bottomley and Mr. Corneel Coens are developers of the EORTC measurement system which is provided to pharmaceutical industries to fund EORTC research but do not have any financial gain from this directly, as the funding is used for research for the EORTC Quality of Life Group, translations, development of new measures and methodology work.

Authors' Contributions

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Data analysis and interpretation: IG, EZ, CC, CQ, FM, VB, KT, DZ, MP, DZ, EN, VBR, FC, MS, GV, AB

Manuscript writing: IG, EZ, CC, CQ, FM, VB, KT, DZ, MP, DZ, EN, VBR, FC, MS, GV, AB

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Acknowledgements

Co-author Vasiliki Balta is currently employed at Breast International Group.

We wish to thank Sheila Scott Sanderson and Cheryl Whittaker for their helpful assistance in editing.

Ethics Committee Approval

Not required