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## Article Type: original article

### An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients (EORTC QLQ-BR23)- EORTC QLQ-BR45

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The study was presented at ESMO 2019 as oral presentation (209 PD).Abstract:

## Abstract:

### Background:

The EORTC QLQ-BR23 was one of the first disease specific questionnaires developed in 1996 to assess quality of life (QoL) in patients with breast cancer (BC). However, since 1996 major changes in BC treatment have occurred, requiring an update of the EORTC BC module. This study presents the results of the Phase I-III update of the QLQ-BR23 questionnaire.

### Patients and methods:

The update of the EORTC QLQ-BR23 module followed standard EORTC guidelines. A systematic literature review revealed 83 potential relevant QoL issues during phases I-II. After shortening the issues list and following interviews with patients and health care providers, 15 relevant issues were transformed into 27 items. The preliminary module was pre-tested in an international, multicentre phase III study to identify and solve potential problems with wording comprehensibility and acceptability of the items. Descriptive statistics are provided. Analyses were qualitative and quantitative. We provide a psychometric structure of the new items.

### Results:

The phase I and II results indicated the need to supplement the original QLQ-BR23 with additional items related to newer therapeutic options. The phase III study recruited a total of 250 patients (12 countries). The final updated Phase III module contains a total of 45 items: 23 items from the QLQ-BR23 and 22 new items. The new items contain two multi-item scales: a target symptom scale (20 items) and a satisfaction scale (2 items). The target symptom scale can be divided into 3 subscales: endocrine therapy, endocrine sexual and skin/mucosa scale.

### Conclusion:

Our work has led to the development of a new EORTC QLQ BR-45 module that builds on the EORTC QLQ-BR23 and provides a more accurate and comprehensive assessment of the impact of new and scalable treatments on patients' QoL. The final phase IV study is currently underway to confirm psychometric properties of the module.

**Key words:** quality of life, patient reported outcome (PRO), breast cancer, module development

**Key Message:** The updated EORTC QLQ BR-45 module provides comprehensive assessment of the impact of the different actual BC treatment options on patients QoL. The final version of the EORTC QLQ-BR45 is currently available for use in clinical practise and is translated into 19 different languages.

## **Introduction**

Breast cancer (BC) is still the most frequent type of cancer in Europe with 21 cases per 100,000 women [1,2,3]. Although the incidence of breast cancer has increased in the last twenty years, the prognosis and outcomes of those patients have changed dramatically, with survival rates increasing to about 78% for  $\geq$  ten years [4]. This improvement means that an increasing number of BC patients will live with short and long-term side effects of disease and therapy. These facts highlight the importance of health related quality of life (HRQoL) assessment in BC patients as an endpoint in clinical studies.

The EORTC QLQ-BR23 was one of the first modules developed to be used in conjunction with the core questionnaire, the EORTC QLQ-C30. Published in 1996, [5] it consists of 23 items and has been translated into more than 60 languages.

In 1997 Brady et al. developed the 44-item instrument called FACT- B (Functional Assessment of Cancer Therapy-Breast ) also designed to measure HRQoL in BC patients . This instrument consists of the core questionnaire FACT-G (the Functional Assessment of Cancer Therapy -General) and the Breast Cancer Subscale (BCS) [6]. It is widely considered that both questionnaires EORTC QLQ BR-23 and FACT -B and their subscales are the standard instruments for measuring quality of life (QoL) in patients with BC [7,8].

Since the beginning of the work on the EORTC QLQ-BR23, more than 20 years ago major advances have been made with regard to diagnostic and therapeutic options. [9].

While tamoxifen therapy only was once the gold standard for hormonal responsive BC therapy in postmenopausal women, aromatase inhibitors (AI) have since become the first choice for patients with the new toxicities such as arthralgia, bone loss, cognitive dysfunction [10,11]. All of these side effects are underrepresented in the EORTC QLQ-BR23. [12,13]. Over the course of the last decade, taxanes and anthracyclines were established as standard chemotherapy (CTX) for BC patients. Also targeted agents constitute a new generation of cancer drugs in BC therapy . The toxicity profile of of CTX and targeted agents significantly impact QoL in BC patients [14,15,16]. New surgical procedures also lead to new impacts on QOL [17].

Given the effects of newer therapeutic options, it was evident that the original 23-item QLQ-BR23 may not be able to cover many important QoL issues and potential side effects. Therefore, the EORTC QLG decided to update this module.

## **Method**

### **Overview**

The EORTC QLG has implemented a four phase methodology in order to develop modules [18]. Phase I involves generating a list of QoL issues relevant for the selected group of patients; Phase II transforms the issues into a provisional questionnaire; Phase III involves pre-testing the questionnaire for relevance and acceptability; as well as preliminary psychometric properties and Phase IV is designed to assess/confirm the psychometric properties of the questionnaire in an international field study.

The present report covers Phases I-III of the study.

The Ethical Committee of the Medical University of Graz, Austria was responsible for the PI's application and approval was granted (EK-Nr. 27-355 ex 14/15). Additionally, local ethical committees approved the study protocol according to the national requirements. The study was registered on clinicaltrials.gov database (ClinicalTrials.gov Identifier: NCT27-355).

### **Phase I: Generating quality of life issues relevant for breast cancer patients**

An extensive literature search for studies using the EORTC QLQ-BR23 was performed, in order to help identify studies reporting potential QoL issues associated with new treatments. A comprehensive search for publications from 01/1995 up to 12/2015 was performed, using databases such as MEDLINE (Pubmed/ProQolid) and the Cochrane Database. Second, analyses of the 115 questionnaires used in studies of HRQoL in BC patients were performed. Third, the investigator brochures of new BC therapies tested in international studies with documentation of the adverse and serious effects were evaluated (a reference lists is available from the corresponding author upon request). Fourth, analyses of the existing issues in the other EORTC QLG modules, [19,20] were examined for possible overlapping issues. International health care professionals (HCP) involved in phase 1 of the study, were invited to discuss the list of issues [21]. Finally, this issue list was administered in 11 study centres /9 countries to BC patients and HCP involved in the treatment of BC. They rated the issues according to their relevance and priority.

### **Phase II**

Based on the outcome of Phase I, relevant issues were transformed into questionnaire items, and according to the EORTC QLQ-C30 format, accompanied by a four-point response scale ranging from "not at all" to "very much". For consistency and whenever possible, items (or wording) of the existing QLQ-BR23 were used and additional items were pulled from the EORTC QLG item library, which currently includes more than 1.500 items (<https://www.eortc.be/itemlibrary/>) [22].

### **Phase III**

#### **Procedure**

A Phase III study was conducted to pre-test the provisional module with the focus on evaluating the importance and acceptability of the questionnaire items.

A structured interview was conducted to evaluate patients' views of the provisional module. Patients were asked if any questions were difficult to answer or understand, confusing, upsetting, offensive, or needed other wording. Patients had the possibility to give their opinion about important items which may not have been included. (Supplement 1). The eligibility was predefined to ensure that subjects adequately represented the target population. Inclusion criteria were: histologically confirmed diagnosis of BC, no previous other primary or recurrent tumors, cognitively able to complete the questionnaires, able to understand the language of the questionnaire, > 18 years of age or above, and provide written informed consent.

The time frames for QoL assessment were chosen so that the symptoms and side effects were more likely to be present and detectable with the module. The sample matrix specifies four main groups according to disease stage by different therapy options. (Supplement 1).

#### **Decision criteria for selecting items**

The following quantitative criteria for were used for deciding to include items:

- item rated difficult to understand or confusing by < 5% of the patients
- item rated difficult to annoying or intrusive by < 5% of the patients
- mean score > 1,5
- prevalence of item scores 3 or 4 in > 30% of the patients
- no floor effect (floor effect exists if > 90% of the patients check 1 or 2)
- no ceiling effect (ceiling effect exists if > 90% of the patients check 3 or 4)
- range > 2 score points on the 1-4 scale
- no missing responses (< 10% of the patients fail to respond to the item).

An item was considered eligible for inclusion if 5 of the 8 criteria were met. *The mean score of >1.5 was compulsory.* In addition to these quantitative criteria we considered qualitative statements by patients in the open interview and judgements by experts of the study group.

## Statistical analyses

Data from BC patients and HCP interviews were analysed using basic descriptive statistics: counts, percentages, means, standard deviations, medians and ranges. We performed preliminary psychometric analyses (Cronbach's alpha) in order to identify a hypothesized scale structure. IBM SPSS Statistics 23.0 was used as the statistical analysis tool.

## Results

### Phase 1

The results of a systematic literature search, along with a search of questionnaires and investigator brochures, yielded an encompassing list of 83 issues (Supplement 2).

A total of 65 international HCP from 14 countries (Austria Italy, Israel, Nederland, Poland, Spain, UK, Sweden, Belgium, France, Portugal, Jordan, Greece and Brazil) representing different disciplines (oncology, surgery, radiotherapy, nursing, clinical psychology) finalize the issue list.

A total of 124 female patients with BC participated in this study. Seventy two percent of the patients were between 36 and 65 years old, 10% were younger than 35, and 18% were older than 65. 53% of the patients had a new diagnosis of BC, 33% of the patients were in follow up, 7% had recurrence and 7% were experiencing disease progression.

*According to recommendations of the EORTC Module Development Manual the following empirical thresholds were applied to consider an issue for inclusion in the list:*

*(a) patients relevance ratings  $\geq 2$  (on the 1 to 4 scale)*

*(b) HCP relevance ratings  $\geq 2$  (on the 1 to 4 scale)*

*(c) patient priority ratings  $\geq 30\%$  (i.e., 30% of the patients agreed that an issue should be included in the list)*

*(d) HCP priority ratings  $\geq 30\%$ .*

*Minimum 1 of the above criteria had to be met, that the issue remains for further analyses.*

As a result, 15 issues were retained for further analysis. (Table 1)

### Phase II

Based on the results of Phase I, relevant issues were transformed into questionnaire items, (described in methods Phase II).

The preliminary module was pre-tested in 12 languages formally conducted according to the EORTC QLG Translation guidelines with a rigorous forward-backward procedure [22.. Debriefing interviews were discussed with a special focus on the order of questions, problems with meaning and new wording. Items were then adapted based on the patients' comments and the discussion with

collaborating HCP. The provisional module consisted of 51 items, 23 items from the EORTC QLQ-BR23 and 28 additional items.

### **Phase III**

#### **Patient characteristics**

A sample of 250 patients participated in this international multicenter study. Patients were recruited from 14 centers /12 countries, representing Northern (Germany, Norway; n = 49 patients), central (Austria, France, Belgium; n=49 patients), Southern (Israel, Italy, Spain, Croatia; n = 99), Eastern (Poland; n = 15), and English-speaking (UK; n = 13) European Countries, and one non-European region (Brazil; n = 25). The clinical characteristics of the patient are shown in Table 2. About two thirds (74.4%) of participating patients were under active treatment and most of the patients (i.e. 84%) were diagnosed less than five years ago. Considering the therapy modality, the patient sample was well balanced. The majority of patients were living with a partner or family and about half of the patients were sexually active (54.4%). The participants were well educated, with 30% completing post-secondary education and 31.3%, university level.

#### **Qualitative and quantitative analyses (responses to open-ended questions)**

In the qualitative portion of the study, the patients responded to the open-ended questions assessing whether some items were missing, difficult to understand or could be deleted. Overall, 111 comments from individual patients were related to different single items. Significant concerns were expressed by patients from Brazil for item #37 (N=10/25). This item was deemed difficult to understand/confusing. Item #37 is part of the QLQ-BR23 and after discussion with the Translation Team at the EORTC, the wording of this item was changed. More than 3 patients felt that items concerning mental condition, 13 (5%), and job 8 (3.2%) were missing and 4 (1.6%) patients stated that an additional issue about side effects was not necessary. Six patients (2.4%) were dissatisfied with the timeframe defined in the questionnaire, especially for the items related to surgery and breast cosmesis. Most comments referred to the group of questions related either to sexuality (#66,67,68,70,71), or satisfaction with the cosmetic results (#79,80). In all instances, patients reported that questions related to sexuality were upsetting/intrusive (2-9). 6 participants reported that #79 was related to “have a surgery”. Thirteen patients (5.2%) felt that questions related to psychological well-being were missing. Because of the existing EORTC spiritually module, we decided not to include additional questions.

#### **Summary of the findings on item selection**

Twenty-two items fulfilled at least 5 of the 8 quantitative inclusion criteria with a mean score > 1.5. (Supplement 3) The results are based on the entire patient sample (N = 250). Results for the target-specific items are based on patients who had received targeted therapy (N=62). We also performed quantitative analyses of the QLQ BR-23. All items fulfilled the inclusion criteria.

In summary, most decisions to exclude items were guided by the principle to avoid redundancies and keep the length acceptable. Thus, the final updated Phase III module contains a total of 45 items, 23 items from the QLQ-BR23 and 22 additional items. We added two blank items so that patients could add symptoms or problems that were not covered in the questionnaire (Supplement 4).

#### **Hypothesized scale structure**

Based on the item content (face validity) and the preliminary psychometric analyses, the following hypothesized scale structure for the new items is proposed: two multi-item scales (target symptom scale (20 items) and satisfaction scale (2 items)). The target symptom scale can be further divided into 3 subscales: endocrine therapy scale, endocrine sexual scale and skin/mucosis scale (Table 3) .

Additional analyses showed no strong correlation with the existing scales of the QLQ-BR23. All scales exceed the accepted threshold of  $\geq 0.70$  Cronbach's alpha. Thus, this underlines the necessity of new subscales to cover all side effects of current BC therapies.

## **Discussion**

Following the standardised approach to updating EORTC QLG modules, the results of our literature review, and interviews with patients and HCP, highlighted the fact that the original QLQ-BR23 should be supplemented by additional items to assess the impact and side effects of different therapeutic modalities on QoL.

In our Phase III study we included 250 patients from 12 countries, representing Northern, central Europe, Southern, Eastern, English-speaking and non-European (Brazil) regions with the aim to test the new items regarding relevance, acceptability, completeness and comprehensibility. The result is an updated module with 45 items, 23 of which are from the original QLQ-BR23 module. The new additional items reflect side effects and symptoms related to new BC therapies that have evolved since the development of the EORTC QLQ-BR23. Grouping the items by face validity and performing psychometric analyses suggest four multi-item scales (target, endocrine, endocrine sexual, skin/mucosis and satisfaction) scales.

Additionally, in light of recent rapid developments in oncology, the new module includes three blank items as an option so that patients can add symptoms or problems that were not covered in the questionnaire. This may be valuable information in an era of rapid development of therapeutic options. These three items are not part of the validation instrument and are one option to collect more information.

One of the major findings of this cross-cultural project was that 23 items of the original QLQ BC-23 fulfilled the quantitative criteria, more than 20 years after their original development. Following the suggestion from patients, the wording of one item had to be changed to be consistent with the EORTC standards.

The scale structure of the EORTC QLQ-BR23 remains unchanged, which ensures comparability between published and ongoing studies using the original and those using the new questionnaire. Now, the new scales are added to the original EORTC QLQ-BR23 and the new breast cancer module called EORTC-BR45. There is the possibility to use some of the scales depending on the aim of the study/research questions, therapy e.g relevance of issues can differ based on therapy modality). The new target scale could be used as one scale or 3 separate scales (depending on the research questions).

The new scales showed no strong correlation with the existing scales of the EORTC QLQ-BR23. Thus, this underlines the necessary for new subscales to cover all side effects of current BC therapy. All scales exceeded the accepted threshold of  $\geq 0.70$  Cronbach's alpha.

In conclusion, our revised tool is named the EORTC QLQ-BR45 questionnaire. This has been developed according to the robust methodology specified in the EORTC QLG guidelines for module [23]. An impressive number of 350 patients and 75 HCP were involved in the development procedure. The final version of the EORTC QLQ-BR45 is currently available for use in clinical trials and practice and is translated in 19 different languages. (Supplement 5) An international, cross-cultural, multicenter phase IV study is currently underway with the focus to confirm the psychometric properties of the module.

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