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ORIGINAL ARTICLE

An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45☆

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Background: The European Organization for Research and Treatment of Cancer (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 and 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 pretested 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 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 (from 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 and a satisfaction scale. The target symptom scale can be divided into three subscales: endocrine therapy, endocrine sexual and skin/mucosa scale.

Conclusion: Our work has led to the development of a new EORTC QLQ-BR45 module that provides a more accurate and comprehensive assessment of the impact of new and scalable treatments on patients' QoL. The final version of the EORTC QLQ-BR45 is currently available for use in clinical practice. The final phase IV study is underway to confirm psychometric properties of the module.

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

INTRODUCTION

Breast cancer (BC) is still the most frequent type of cancer in Europe with 21 cases per 100 000 women.[1–3] Although the incidence of BC has increased in the last 20 years, the prognosis and outcomes of those patients have changed dramatically, with survival rates increasing to ∼78% for ≥10 years.[4] This improvement means that an increasing number of patients with BC will live with short- and long-

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term side-effects of disease and therapy. These facts highlight the importance of health-related quality of life (HRQoL) assessment in these patients as an end point in clinical studies.

The European Organization for Research and Treatment of Cancer (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 >60 languages.

In 1997 Brady et al. developed the 44-item instrument called FACT-B (the Functional Assessment of Cancer Therapy-Breast) which was also designed to measure HRQoL in patients with BC. This instrument consists of the core questionnaire FACT-G (the Functional Assessment of Cancer Therapy-General) and the Breast Cancer Subscale.[6] It is widely considered that both questionnaires (EORTC QLQ-BR23 and FACT-B) and their subscales are the standard instruments for measuring QoL in patients with both early and metastatic BC.[7,8]

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

Whereas tamoxifen therapy alone was once the gold standard for hormonal-responsive BC therapy in postmenopausal women, aromatase inhibitors have since become the first choice for patients with new toxicities such as arthralgia, bone loss and 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 patients with BC. In addition, targeted agents constitute a new generation of cancer drugs in BC therapy. The toxicity profile of the CTX and targeted agents significantly impact QoL in patients with BC.[14–16]

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 Quality of Life Group (QLG) decided to update this module.

METHODS

Overview

The EORTC QLG has implemented a four-phase methodology 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 pretesting 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 principal investigator's application and approval was granted (EK-Nr. 27-355 ex 14/15). In addition, 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 QoL issues relevant for patients with BC

An extensive literature search for studies using the EORTC QLQ-BR23 was performed, to help identify studies reporting potential QoL issues associated with new treatments. First, a comprehensive search for publications from January 1995 up to December 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 patients with BC 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 list 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 (HCPs) 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 patients with BC 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 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 >1500 items.[22]

Phase III

Procedure. A phase III study was conducted to pretest 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 that may not have been included. The eligibility was predefined to ensure that participants adequately represented the target population. Inclusion criteria were histologically confirmed diagnosis of BC, no previous history of other primary or recurrent tumours, cognitively able to complete the questionnaires, able to understand the language of the questionnaire, ≥18 years of age, and able to 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 (supplementary Table S1, available at *Annals of Oncology* online).

Decision criteria for selecting items. The following quantitative criteria 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 five of the eight 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 patients with BC 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) to identify a hypothesized scale structure. IBM SPSS Statistics 23.0 (IBM, New York, NY) 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 (supplementary Table S2, available at *Annals of Oncology* online).

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

A total of 124 female patients with BC participated in this study; 72% of the patients were between 36 and 65 years of age, 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:

- patients relevance ratings ≥2 (on the 1 to 4 scale)
- HCP relevance ratings ≥2 (on the 1 to 4 scale)
- patient priority ratings ≥30% (i.e. 30% of the patients agreed that an issue should be included in the list)
- HCP priority ratings ≥30%.

At least one of the aforesaid criteria had to be met for the issue to analysed further. Eventually, 15 issues were retained for further analysis (Table 1).

Phase II

Based on the results of phase I, relevant issues were transformed into items (described in the Methods section, Phase II subsection).

Table 1. Decision for including or excluding issues

No.	Issue	Relevance		Priority for inclusion		Criteria
		HCP rating (n = 65), mean	Patient ratings (n = 124), mean	HCP ratings (n = 65), %	Patient ratings (n = 124), %	Fulfilled
01	Night sweating	3.03	2.53	43.1	39.5	4 of 4
02	Cold sweat	2.70	1.83	21.5	16.9	1 of 4
03	Cognitive functions	3.40	2.45	56.9	57.3	4 of 4
04	Mood	3.56	2.83	61.5	66.9	4 of 4
05	Light-headedness/dizziness	2.65	2.11	16.9	33.1	3 of 4
06	Mucositis/stomatitis	3.21	1.88	50.8	25.0	2 of 4
07	Hand-foot syndrome	3.08	1.81	41.5	28.2	2 of 4
08	Loss of feelings in fingers/paraesthesia	3.51	2.16	55.4	42.7	4 of 4
09	Joint stiffness	3.46	2.18	58.5	37.1	4 of 4
10	Bone pain	3.39	2.50	43.1	57.3	4 of 4
11	Skeletal complications/muscle discomfort	3.41	2.43	47.7	47.6	4 of 4
12	Bladder problems	2.57	1.80	21.5	27.4	2 of 4
13	Dryness of vagina	3.32	2.00	53.8	30.6	4 of 4
14	Weight gain	3.44	2.17	60.0	28.2	3 of 4
15	Breast cosmesis/cosmesis results	3.55	2.41	58.5	55.6	4 of 4

Inclusion criteria as follows. Relevance: HCP ratings, mean ≥2; patient ratings, mean ≥2. Priority for inclusion: HCP ratings >30%; patient ratings >30%.
HCP, health care professional.

The preliminary module was pretested in 12 languages formally translated according to the EORTC QLG Translation guidelines[22] with a rigorous forward—backward procedure.[23] 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 multicentre study. Patients were recruited from 14 centres/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 patients are presented in Table 2. About two-thirds (74.4%) of participating patients were under active treatment and most (i.e. 84%) were diagnosed <5 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 postsecondary 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. Thirteen patients (5%) felt that items concerning mental condition are missing. Eight patients (3.2%) missed items concerning job. Four patients (1.6%) stated that an additional issues 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 to satisfaction with the cosmetic results (#79 and 80). In all instances, patients reported that questions related to sexuality were upsetting/intrusive (#2—9). Six 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 spiritual well-being module, we decided not to include additional questions.

Summary of the findings on item selection. Twenty-two items fulfilled at least five of the eight quantitative inclusion criteria with a mean score >1.5. (supplementary Table S3, available at *Annals of Oncology* online) The results are

Table 2. Patient characteristics (phase 3 study; $N = 250$)

Status of disease	*n*	%
Newly diagnosed	137	54.8
No evidence of disease	82	32.8
Recurrence	27	10.8
Missing	4	1.6
Years since diagnosis		
<5 years	210	84.0
≥5—10 years	24	9.6
>10 years	13	5.2
Missing data	3	1.2
Treatment status		
Active treatment	186	74.4
No active treatment	62	24.8
Missing	2	0.8
Menopausal status		
Pre-menopausal	59	23.6
Post-menopausal	150	60.0
Treatment-related menopause	28	11.2
Unknown	11	4.4
Missing	2	0.8
TNM classification		
T0[a]	9	3.6
T1	99	39.6
T2	77	30.8
T3	22	8.8
T4	17	6.8
Tis	14	5.6
Missing	12	4.8
N0	134	53.6
N1	76	30.4
N2	21	8.4
N3	7	2.8
Missing	12	4.8
M0	212	84.8
M1	23	9.2
Missing	15	6.0
Surgery		
BCT	104	41.6
OPBC	13	5.2
Simple mastectomy	49	19.6
Mastectomy and reconstruction	47	18.8
Missing	37	14.8
Sentinel node biopsy	91	36.4
Axillary dissection	92	36.8
No axillary operation	28	11.2
Missing	39	15.6
Unknown	11	4.4
Systemic therapy		
Chemotherapy		
Anthracycline	95	62.1
Taxane	110	71.9
Carboplatin	6	3.9
Capecitabine	8	5.2
Vinorelbine	5	3.3
Gemcitabine	8	5.2
Cyclophosphamide	99	64.7
Others	35	22.9
Target therapy		
Trastuzumab	52	82.5
Pertuzumab	16	25.4
T-DM1	1	1.6
Everolimus	3	4.8
Bevacizumab	2	3.2
Lapatinib	1	1.6
Olaparib	1	1.6
Palbociclib	2	3.2
Bisphosphonate	6	9.5
Hormonal therapy		
Aromatase inhibitors	91	71.1
Fulvestrant	7	5.5

Continued

Table 2. Continued

Status of disease	*n*	%
Gonadotropin-releasing hormone analogue	8	6.3
Tamoxifen	65	50.8
Others	9	7.0
Radiotherapy		
WBI	82	62.6
WBI with axillary irradiation	38	29.0
APBI	5	3.8
IORT	3	2.3
Others	7	5.3

APBI, accelerated partial-breast irradiation; BCT, breast conserving surgery; IORT, intraoperative irradiation; OPBC, oncoplastic breast conserving surgery; WBI, whole-breast irradiation.
[a] After neoadjuvant chemotherapy.

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-BR23. 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 (supplementary Table S4, available at *Annals of Oncology* online).

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 three 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.

Table 3. Hypothesized scale structure of the EORTC QLQ-BR45

Scale	Item number
Functional scales/items	
Body image	39–42
Future perspective	43
Sexual functioning	44, 45
Sexual enjoyment	46
Breast satisfaction	74, 75
Symptom scales/items	
Systemic therapy side-effects	31–34, 36–38
Upset by hair loss	35
Arm symptoms	47–49
Breast symptoms	50–53
Target therapy scale	
Endocrine therapy symptoms	54–56, 63–69
Skin mucosis symptoms	57–62
Endocrine sexual symptoms	70–73

EORTC, European Organization for Research and Treatment of Cancer.

DISCUSSION

Following the standardized 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, Southern, Eastern, and English-speaking European regions and one non-European (Brazil) region 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 initial psychometric analyses suggest four multi-item scales: endocrine, endocrine sexual, skin/mucosis (target) and satisfaction scales.

In addition, in light of recent rapid developments in oncology, the new module includes two 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 two 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-BR23 fulfilled the quantitative criteria, >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 BC module called EORTC-BR45. There is the possibility to use some of the scales depending on the aim of the study/research questions and therapy, as relevance of issues can differ based on therapy modality. The new target scale could be used as one scale or three 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 into 19 different languages (supplementary Table S5, available at *Annals of Oncology* online). An

international, cross-cultural, multicentre phase IV study is currently underway with the focus to confirm the psychometric properties of the module.

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DISCLOSURE

VB-R, KK, RAC, TC, ECI, SS, MP, JW, OM, GLA, KAT, PS, MS, NA, GV, EG and JA are members of the EORTC Quality of Life Group. FC, DC, EB, KP are members of the EORTC Breast Cancer Group. AB is an employee of the EORTC.

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