Supportive Care in Cancer (2019) 27:4123–4132
https://doi.org/10.1007/s00520-019-04698-0

ORIGINAL ARTICLE

PROMs following breast-conserving therapy for breast cancer: results from a prospective longitudinal monocentric study

I. Kindts[1,2] · A. Laenen[3] · M. van den Akker[4,5] · C. Weltens[1,2]

Received: 17 May 2018 / Accepted: 11 February 2019 / Published online: 21 February 2019

Abstract

Background Treatment of breast cancer includes many options and shared decision making is becoming standard practice. Within the context of treatment individualization, the omission of radiotherapy (RT) can be considered. It is thereby of great importance to correctly foresee the side effects attributed to RT. Data from longitudinal studies with contemporary techniques however are sparse. The purpose of the present study was to evaluate patient-reported outcome measures (PROMs) and long-term aesthetic outcome (AO) related to RT in the breast-conserving therapy (BCT) setting for breast cancer over time.

Methods Patients treated with BCT between April 2015 and April 2016 were prospectively included in the cohort. Evaluations were made at six time points: at baseline (before RT), during and at the end of RT, between 3 and 6 months, 1 year and 2 years after RT. AO was scored by the patient and by the BCCT.core software. Further PROMs were measured with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30/-BR23 and the Body Image after Breast Cancer Questionnaire BIBCQ. Patients were evaluated over 2 years. First, we assessed the evolution in time. Second, we tested the differences in mean scale scores of the PROMs between patients with a favourable and an unfavourable AO.

Results One hundred seventy-five patients were included in the analysis. At baseline, unsatisfactory levels were already present for several scales. Most unsatisfactory PROMs improved up to 1 year after RT. Complaints of fatigue increased at the start but decreased up to a lower level than that at baseline up to 1 year after RT (mean difference (MD) 7.6, − 12.3, respectively). Cognitive functioning showed a small decrease at the start with no further significant decrease (MD − 4.73, − 0.21, respectively). Breast symptoms significantly increased during RT but decreased afterwards up to 2 years after RT to lower values than those at baseline and were then considered satisfactory (MD 15.6, − 19.7, − 4.1, respectively). AO scored as PROM associated with BCCT.core and with the body image measures.

Conclusions The study suggests that quality of life and body image are temporarily impaired due to RT. Around one third of patients score their long-term AO as unfavourable. These results should be discussed with the patient and could help in the decision making of the treatment plan and in the clarification of the patient's expectations.

Keywords Breast-conserving therapy · Breast cancer · PROMs · Aesthetic outcome

✉ I. Kindts
Isabelle.kindts@uzleuven.be

[1] Department of Oncology, Experimental Radiation Oncology, KU Leuven–University of Leuven, B-3000 Leuven, Belgium

[2] Department of Radiation Oncology, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium

[3] Leuven Biostatistics and Statistical Bioinformatics Centre (L-Biostat), KU Leuven University, Kapucijnenvoer 35, B-3000 Leuven, Belgium

[4] Department of Family Medicine, School CAPRI, Maastricht University, Maastricht, The Netherlands

[5] Academic Center for General Practice, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

Introduction

With an incidence rate of approximately 1.7 million per year, breast cancer is the most common form of cancer in women [1]. Due to early detection, improved treatment and strict follow-up, the oncological outcome of breast cancer patients has improved in the last decades, resulting in a growing number of long-term survivors [2]. Breast cancer requires a multidisciplinary approach with any combination of surgery, radiotherapy (RT) and systemic therapy, depending primarily on the clinical stage.

The majority of breast cancer patients present at an early stage. Population-based studies have shown that around 60 to

70% of breast cancer patients are treated with breast-conserving therapy (BCT) [3, 4]. This includes breast-conserving surgery followed by RT and is the cornerstone for locoregional treatment since randomised trials have shown equal survival rates in early-stage breast cancer patients compared to mastectomy [5, 6]. By adding RT to the breast-conserving surgery, the 10-year recurrence rate decreases from 35 to 19% and the 15-year breast cancer survival rate improves by almost 4 to 79% [7]. Recent advances in RT have resulted in decreased treatment lengths and side effects while maintaining efficacy within a broad range of treatment modalities. Additionally, although the absolute local recurrence risks without RT have been reported as high as 20 to 40%, clinical trials have tried to identify low-risk patients in whom the absolute effect of RT is modest and RT might thus be omitted [8]. Besides cost cutting, the underlying drive of this treatment de-escalation arises from the increased survival rates with a growing interest in quality of survival. Long-term side effects of RT on cardiac and pulmonary tissue as well as on secondary malignancies have long been the main area of interest [9, 10]. In recent years, more and more attention was paid to long-term aesthetic outcome (AO) and health-related quality of life (QOL): the patient's physical, psychological and social response to the disease and its treatment [11]. Furthermore, more consideration has been given to patient-reported outcome measures (PROMs), comprising health-related QOL and also broader concepts such as patient satisfaction with care [12]. The use of PROMs is essential to actually understand the effects and outcomes of the treatment from the patient's point of view.

Nearly 50% of women treated for early-stage breast cancer experience the toxicities they perceive as severe or very severe, and factors not related to RT appear to have the biggest impact [13, 14]. Within the context of treatment individualization and the omission of RT, it is however important to correctly foresee side effects related to RT. PROMs related to breast RT have been investigated and patient-reported late breast adverse effects attributed to RT include skin changes, breast shrinkage, breast hardness and suboptimal AO, which negatively impact the psychosocial well-being [15]. However, data from longitudinal studies with contemporary techniques such as intensity-modulated radiotherapy are sparse. It is furthermore known that the toxicity burden faced by the patients may be greater than acknowledged by physicians [16]. In clinical practice therefore, women are generally well informed on the acute toxicities of treatments. Since limited information is available on the long-term physical and psychosocial sequelae of treatment, nor of the recovery, ignorance for late side effects remains an issue [17].

Given the variety of treatment modalities and the upcoming trend to evaluate de-escalation, shared decision making is of paramount importance. Thereby, the patient's voice is put at the forefront of health care delivery and data-driven patient education comparing PROMs between treatment options can help. A crucial first step in this process is to define treatment goals. Those goals can be any combination of oncological outcomes such as recurrences or survival, side effects and quality of life. Secondly, the parameters influencing those oncological outcomes, such as clinical symptoms, genetics or imaging, should be determined and data state these numbers are increasing [18]. Discussing PROMS with the patient will not only contribute to the decision making when weighing up pros and cons on symptoms and side effects of treatment, it will also prepare women for the treatment experience, help identify patients at risk and enable early interventions [13]. Describing the patterns, correlates and frequencies of treatment-associated toxicities from a large population-based sample allows clinicians thereby to understand the actual patient's treatment experience outside rigorously conducted clinical trials.

The purpose of the present study was to gain knowledge on PROMs related to RT in the BCT setting. Also, we wanted to evaluate long-term AO scored by the patient and by an objective measurement tool. Furthermore, the agreement between PROMs and AO measures was explored. We have therefore prospectively and longitudinally followed a group of 175 patients for 2 years, treated with BCT in a monocentric setting.

Material and methods

Patient cohort

The population of this prospective cohort study was composed inviting all consecutive patients treated with BCT for breast cancer with curative intent who consulted the RT department at the University Hospitals Leuven, Belgium, between April 2015 and April 2016. Informed consent was obtained. Patient-, tumour- and treatment-related characteristics were prospectively collected.

BCT included whole-breast irradiation followed by a boost to the tumour bed. Two fractionation schedules were applied for whole-breast irradiation: normofractionation (50 Gy in 25 fractions) and hypofractionation (42.56 Gy in 16 fractions). For the boost, either 16 Gy in 8 fractions or 13.3 Gy in 5 fractions was applied with electrons or photons. High dose rate brachytherapy dose was 8.5 Gy. For the selection of the boost technique, an in-house developed flowchart based on the depth of the tumour bed was used. For a clinical target volume lying more than 28 mm beneath the epidermis, an interstitial boost was chosen over an electron boost because of skin doses. If the patients refused a brachytherapy boost, or if it was technically impossible, a photon boost was suggested [19]. Treatment regimens were discussed at the multidisciplinary tumour board and discussed with the patient. Regional nodal irradiation was allowed. Hormonal therapy included

tamoxifen and aromatase-inhibitors in different regimens and was prescribed in hormone receptor-positive breast cancer patients. Chemotherapy was given according to standard protocol and mostly included epirubicin, cyclophosphamide and taxanes.

The study was approved by the Clinical Trial Centre and the Ethical Committee of our institution.

PROMs

Several tools have been used for the measurement of PROMs in patients with a history of breast cancer [20]. In 2017, the International Consortium for Health Outcomes Measurement has developed a standard set of value-based PROMs for breast cancer [21]. Based on this guideline and the review by Kanatas et al. and Chen et al., the EORTC QLQ-C30 and -BR23 and the BIBCQ were used as reliable cancer-related QOL and body image–related questionnaires [20–22].

Quality of life

The QLQ-C30 was developed as a cancer-specific QOL questionnaire. It has 30 items that form five functional scales (physical, role, emotional, cognitive and social), a global QOL scale, three symptom scales (fatigue, pain and nausea-vomiting), five single-item symptom measures (dyspnoea, insomnia, appetite loss, constipation and diarrhoea), and one financial impact question. These are coded with the same response categories (scored 1 to 4): 'not at all', 'a little', 'quite a bit' and 'very much'; except for the global QOL scale, which is scored as a visual analogue scale ranging from 1 (very bad) to 7 (excellent). All the scales and single-item scores are transformed to range from 0 to 100. A high score for a functional scale or global QOL indicates better levels of functioning and/or global QOL, with a score above 80 considered to be satisfactory. A high score for a symptom scale or item represents a high level of symptoms or problems, with a score below 20 considered to be satisfactory [23]. For the interpretation of the changes over time, the Evidence-Based Interpretation Guidelines (EBIG) for longitudinal studies were used where improvements or deteriorations are classified as trivial, small, medium or large. Separate thresholds are thereby used for the different subscales: for global QOL for example, a decrease in score from 5 to 10 points indicates small deteriorations, from 10 to 16 medium deteriorations and more than 16 large deteriorations [24].

Body image

The QLQ-BR23 module consists of 23 items assessing disease symptoms, side effects related to different treatment modalities (surgery, chemotherapy, radiotherapy and hormonal therapy), body image, sexual functioning and future perspective. It incorporates five domains: body image, systemic therapy side effects, breast symptoms, arm symptoms and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective. The scoring approach is identical to that for the functioning and symptom scales and for the single items in the QLQ-C30 [25]. Clinical significance is interpreted according to Osaba et al.: the mean differences from 5 to 10 points can be considered minimal, from 10 to 20 points intermediate, and more than 20 points large [26].

The Body Image after Breast Cancer Questionnaire (BIBCQ) was designed specifically to measure the long-term impact of breast cancer on body image in a multidimensional fashion. It is a measure with a 53-item questionnaire comprising six optional items specific to women with two breasts [27]. The BIBCQ is suggested in the evaluation of various treatment forms for breast cancer [22].

Aesthetic outcome

Besides the three questionnaires, PROMs were also assessed for AO: patients were asked to score their AO according to Harris et al. as excellent, good, fair or poor [28].

Objective aesthetic outcome analysis

An anterior view picture of the patient was taken with the patients hands on the hips. The BCCT.core software was used to evaluate the AO. Based on the semi-automatic localization of fiducial points (nipple complex, breast contour, sternal jugular notch, mark 25 cm downwards from the jugular notch), the software firstly measures asymmetry, skin colour changes and surgical scar appearance. Secondly, the set of measures is automatically converted into an overall objective AO: excellent, good, fair or poor [29].

Follow-up

Patients were evaluated at six preset time points: (1) at baseline, this is after surgery and before the start of radiotherapy; (2) before the start of the boost, this is during RT; (3) at the end of radiotherapy; (4) between 3 and 6 months after radiotherapy; (5) 1 year after radiotherapy; and (6) 2 years after radiotherapy. No photographs were taken at the end of RT because of the acute breast changes immediately after the removal of interstitial needles in case of a brachytherapy boost. Patients scored their AO at baseline and 2 years after RT.

Statistical analysis

AO scored by the patient or measured by the BCCT.core software was dichotomized in excellent/good ('favourable') versus fair/poor ('unfavourable'). Linear models were used for the analysis of continuous or ordinal scale scores. Logistic

regression was used for the analysis of the binary AO score. A random intercept for patient was modelled to account for the longitudinal structure of the data. First, we assessed the evolution in time of the PROMs and AO. Second, we wanted to assess whether the difference in mean scale scores of the PROMs differed between patients with a favourable and an unfavourable AO. We therefore tested their main effects for AO.

Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

Results

Patient cohort

One hundred seventy-five patients were included in the analysis; 4 patients refused participation. Patient characteristics are available in Table 1. The number of patient evaluations at different time points is described in Table 2.

Evolution of PROMs and AO over time

The mean scores of the functional and symptom scales of the QOL-C30, QLQ-BR23 and BIBCQ at all time points are reported in Table 3. At baseline, the mean QLQ-C30 scores for global QOL, role and emotional functioning, fatigue, pain and insomnia as well as the mean QLQ-BR-23 scores for sexual enjoyment, future perspectives, breast symptoms and upset by hair loss showed unsatisfactory outcomes (mean scores lower than 80 or higher than 20 [23]).

Global QOL showed trivial deteriorations during RT and a medium improvement thereafter up to 1 year after RT to higher levels than at baseline, however still unsatisfactory (mean difference (MD) − 3.8, 8.7 and p 0.009, < 0.001, respectively) (Fig. 1a). A similar pattern was seen for physical functioning (MD − 2.4, 4.6 and p 0.021, < 0.0001, respectively) with persistent satisfactory overall scores and differences considered as small improvements after RT. For role, emotional and social functioning, no difference was seen during RT with an increase afterwards up to 1 year after RT, all attaining satisfactory levels (MD 13.2, 5.5, 10.0 and $p < 0.001$, 0.0015, < 0.001 respectively) (Fig. 1b). Medium improvements were obtained for role and social functioning. Fatigue showed a small deterioration at the beginning of RT, but a medium improvement thereafter up to 1 year after RT (MD 7.6, − 12.3, respectively and $p < 0.001$) (Fig. 1c). Pain and insomnia did not significantly change during RT, but showed a small, significant improvement thereafter up to 1 year after RT (MD − 6.5, − 5.9 and $p < 0.001$, 0.012, respectively). Insomnia scores thereby remained at an unsatisfactory level. Nausea and vomiting, dyspnoea and appetite loss worsened at the beginning of RT but improved towards no difference with baseline 2 years after RT (MD 3.7, 0.8 and $p < 0.001$, 0.374, respectively; MD 5.0, 0.6 and p 0.005, 0.750, respectively and MD 5.1, − 2.7 and p 0.002, 0.109, respectively) with continuously satisfactory scores. The initial loss of appetite was considered small; all other changes for appetite loss were trivial. Cognitive functioning showed a small deterioration at the beginning of RT with no further significant decrease (MD − 4.73, − 0.21 and p 0.003, 0.894, respectively).

Breast symptoms significantly increased during RT but decreased afterwards up to 2 years after RT to lower values than at baseline which are then considered satisfactory (MD 15.6, − 19.7, − 4.1 and $p < 0.001$, < 0.001, 0.005, respectively) (Fig. 2a). Future perspective increased minimally from baseline to 1 year after RT without further changes (MD 6.1, − 1.0 and p 0.001, 0.603, respectively). There were no to minimal changes in body image, sexual functioning, systemic therapy side effects and arm symptoms, and all scores but sexual functioning remained satisfactory.

Limitations globally decreased from baseline to 2 years after RT; there was an increase during RT but then a decrease up to 1 year after RT and no further change up to 2 years after RT (MD − 1.4, 1.0, − 2.5, 0.1 and $p < 0.001$, 0.013, < 0.001, 0.747 respectively) (Fig. 2b). Body stigma changed significantly over time: a decrease was seen comparing baseline with 1 year after RT; however, this was normalised when comparing baseline with 2 years after RT (MD − 1.6, − 0.4 and p 0.001, 0.466, respectively). A similar pattern was observed for transparency (MD − 0.5, − 0.3 and p 0.017, 0.200, respectively).

There were no significant changes over time for the other QLQ-C30, QLQ-BR23 or BIBCQ measurements.

Six patients (3.43%) scored their AO as unfavourable at baseline and 53 patients (31.36%) 2 years after RT. Three patients (1.71%) had unfavourable AO measured by BCCT.core at baseline, 37 (21.39%) during RT, 33 (19.41%) at the end of RT, 43 1 year after RT (20.61%) and 47 patients 2 years after RT (27.81%).

Relationship of PROMs and AO

The QLQ-BR23 body image scores were associated with the AO scored by the patient (p 0.032) (Fig. 3a). A significant association also was found for the BIBCQ body stigma, body concern and transparency scale (p 0.001, < 0.001 and 0.026, respectively). Concerning AO measured with BCCT.core, a significant association was found for the QLQ-BR23 body image and breast symptom scores (p 0.017 and 0.043, respectively) and for the BIBCQ body stigma, body concern and transparency scores (p 0.035, 0.029 and 0.031, respectively) (Fig. 3b). There was no association between AO and the QLQ-C30, nor with the other QLQ-BR23 or BIBCQ domains.

AO scored by the patient was significantly associated with AO measured by the BCCT.core ($p < 0.001$) at both time points.

Table 1 Patient characteristics

Characteristic		Median	IQR
Age		58.0	51.0; 65.0
Breast cup		C	B; D
Breast band size (EU size)		80	75; 85
Characteristic		*n*	%
Menopausal status	Premenopause	33	18.86
	Perimenopause	7	4.00
	Postmenopause	135	77.14
BMI	< 20	15	8.57
	20–25	75	42.86
	25–30	63	36.00
	> 30	22	12.57
Smoking	Never/stopped	143	81.74
	Current	32	18.29
Alcohol	Never/stopped	44	25.14
	Current	131	74.86
Diabetes	No	168	96.00
	Yes	7	4.00
Arterial hypertension	No	132	75.43
	Yes	43	24.57
Side	Left	88	50.29
	Right	87	49.71
Chemotherapy	No	127	72.57
	Yes	48	27.43
Hormonal therapy	No	23	13.14
	Yes	152	86.86
Trastuzumab	No	156	89.14
	Yes	19	10.86
Lymphadenectomy	None	23	13.14
	Sentinel	129	73.71
	ALND	23	13.14
Section margins	Negative	164	93.71
	Positive	11	6.29
Position of tumour	Upper inner	38	21.71
	Upper outer	98	56.00
	Lower inner	18	10.29
	Lower outer	19	10.86
	Retro-areolar	2	1.14
Re-resection	No	127	72.57
	Yes	48	27.43
Seroma	No	127	72.57
	Yes	48	27.43
Target volume	Breast only	123	70.29
	Breast and regional nodes	52	29.71
Characteristic		Mean	Range
Surgical specimen weight wide excision (g)		31.2	1.0;101.0
Surgical specimen weight axillary lymph node dissection (g)		93.9	29.0;181.0
Pathological tumour size invasive + in situ (mm)		18.0	0.0;55.0

ALND axillary lymph node dissection

Table 2 Patient evaluations

	Baseline	During RT	End of RT	3–6 months after RT	1 year after RT	2 years after RT
QLQ-C30	175	173	172	169	175	172
QLQ-BR23	175	173	172	169	175	172
BIBCQ	174	173	170	170	167	169
AO (PROM)	175	/	/	/	/	170
AO (BCCT.core)	175	173	/	170	165	170

QLQ-C30, QLQ-BR23 and BIBQ: questionnaires on quality of life and body image. BCCT.core: software to score AO based on photographs. *AO* aesthetic outcome, *PROM* patient-reported outcome measure

Table 3 Mean values and standard deviations of QOL-C30, QLQ-BR23 and BIBCQ scores at different time points

	Baseline	During RT	End of RT	3–6 months after RT	1 year after RT	2 years after RT
Domain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
QOL-C30						
Global QOL	**67.0 (18.4)**	**64.9 (17.0)**	**63.2 (19.4)**	**67.5 (19.1)**	**71.9 (17.0)**	**70.0 (18.1)**
Physical functioning	84.2 (18.1)	80.7 (17.2)	82.0 (16.6)	81.7 (18.0)	86.4 (15.5)	85.5 (16.7)
Role functioning	**73.0 (27.2)**	**72.0 (26.4)**	**70.4 (27.6)**	**75.6 (24.7)**	83.4 (21.6)	82.8 (23.5)
Emotional functioning	**74.2 (22.3)**	**74.5 (22.7)**	**73.8 (20.4)**	**75.2 (22.5)**	**79.4 (20.0)**	**78.0 (21.4)**
Cognitive functioning	83.9 (22.0)	**79.1 (22.5)**	**78.6 (23.7)**	**78.1 (23.9)**	80.5 (23.3)	**78.7 (24.4)**
Social functioning	82.0 (23.4)	80.6 (22.5)	**79.7 (24.7)**	83.6 (21.2)	89.8 (16.9)	88.1 (18.6)
Fatigue	**31.6 (24.7)**	**39.3 (25.1)**	**37.8 (25.3)**	**33.7 (26.0)**	**26.9 (24.1)**	**28.9 (24.9)**
Nausea and vomiting	2.5 (7.4)	6.2 (12.5)	4.0 (9.5)	3.6 (9.9)	2.5 (8.0)	3.3 (9.5)
Pain	**22.5 (23.8)**	**22.2 (23.4)**	**25.7 (23.5)**	**21.2 (22.5)**	19.0 (21.6)	17.4 (22.4)
Dyspnoea	12.4 (22.4)	17.3 (23.5)	18.6 (24.3)	18.5 (25.5)	12.8 (24.4)	13.3 (23.8)
Insomnia	**31.0 (29.4)**	**33.7 (31.2)**	**31.2 (28.2)**	**30.8 (30.9)**	**25.3 (29.7)**	**29.8 (31.1)**
Appetite loss	8.4 (18.7)	13.6 (22.2)	13.3 (23.1)	8.1 (18.7)	5.0 (15.2)	5.8 (17.9)
Constipation	9.0 (20.0)	9.5 (19.6)	7.9 (17.9)	11.5 (22.8)	9.9 (18.0)	11.5 (22.4)
Diarrhoea	5.5 (15.6)	6.4 (15.9)	4.9 (13.9)	5.3 (16.0)	3.4 (11.9)	4.7 (13.2)
Financial difficulties	7.6 (19.2)	8.6 (19.3)	8.9 (19.7)	9.0 (20.5)	9.0 (21.0)	9.0 (20.4)
QLQ-BR23						
Body image	84.3 (21.2)	86.4 (17.8)	86.5 (17.4)	89.2 (15.7)	88.7 (17.1)	85.9 (26.8)
Sexual functioning	**79.6 (22.2)**	**78.2 (21.5)**	**77.0 (23.6)**	**76.4 (22.7)**	**72.8 (23.8)**	**76.3 (21.5)**
Sexual enjoyment	**51.7 (27.5)**	**47.8 (27.2)**	**47.6 (29.4)**	**47.3 (26.3)**	**42.8 (28.5)**	**42.6 (27.7)**
Future perspective	**55.4 (25.9)**	**60.1 (24.3)**	**58.1 (25.6)**	**56.7 (27.4)**	**61.5 (26.1)**	**60.6 (26.8)**
Systemic therapy side effects	16.2 (15.4)	17.9 (14.4)	18.0 (13.5)	18.6 (14.5)	16.4 (12.6)	16.5 (13.9)
Breast symptoms	**22.2 (20.1)**	**34.8 (20.9)**	**37.6 (19.6)**	**25.8 (17.3)**	**21.0 (16.5)**	18.0 (15.1)
Arm symptoms	17.7 (20.2)	14.8 (19.0)	12.6 (16.7)	18.3 (20.4)	17.0 (18.9)	12.6 (14.8)
Upset by hair loss	**31.1 (38.1)**	**28.1 (33.4)**	**23.8 (32.3)**	**26.8 (35.6)**	**30.5 (32.5)**	**32.6 (34.8)**
BIBCQ						
Vulnerability	31.1 (8.3)	30.7 (8.7)	31.2 (8.5)	30.7 (9.3)	30.2 (8.9)	30.3 (9.2)
Body stigma	33.6 (9.1)	33.1 (9.8)	33.4 (9.1)	32.2 (9.4)	31.6 (9.3)	33.2 (10.0)
Limitations	20.6 (6.3)	21.3 (6.6)	21.6 (6.3)	20.7 (7.1)	19.0 (6.7)	19.3 (7.0)
Body concerns	15.8 (5.2)	15.7 (5.1)	15.4 (5.1)	15.8 (5.4)	15.6 (5.8)	15.8 (5.6)
Transparency	9.1 (3.5)	9.2 (3.8)	9.5 (3.7)	8.6 (3.6)	8.5 (3.5)	8.8 (3.7)
Arm concerns	9.9 (3.8)	9.9 (3.5)	10.1 (3.5)	10.1 (3.9)	9.8 (3.5)	9.8 (3.7)

RT radiotherapy. Unsatisfactory scores for the QLQ-C30 and QLQ-BR23 are indicated in bold

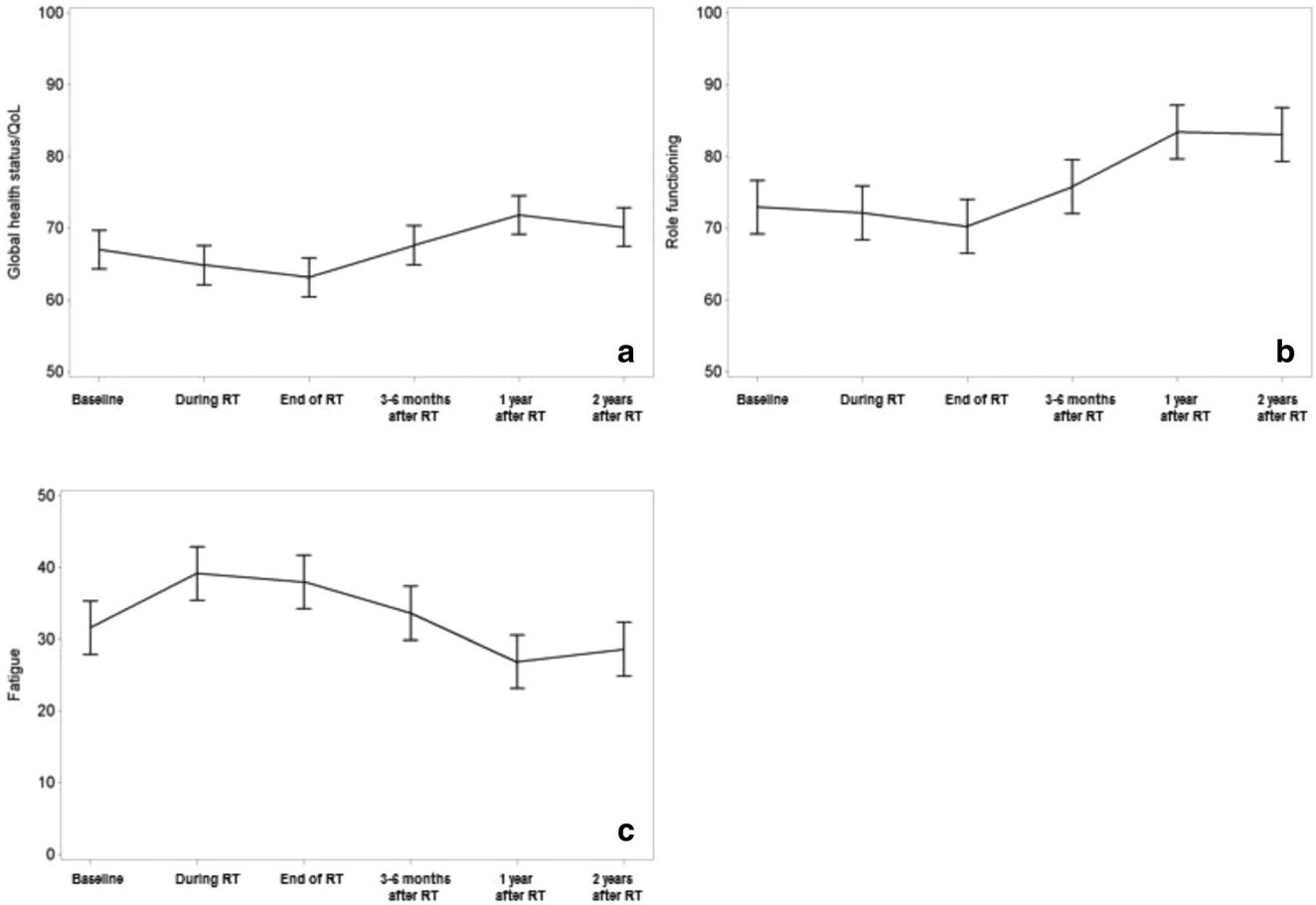

Fig. 1 Global health status (**a**), role functioning (**b**) and fatigue (**c**) over time. Note that the *y*-axis does not show the full range of 0–100

Discussion

Small fatigue/cognitive impairment and intermediate body image disturbances during RT

The first aim of the present study was to evaluate PROMs and long-term AO related to RT in the BCT setting. Important to remark is that, at baseline, unsatisfactory levels were already present for several global, functional, symptom and body image scales. The main causative factors reported in literature are chemotherapy, a young age, the surgical procedure, a large breast volume and antihormonal therapy [13, 14, 30, 31]. The results of the present study show that most of the global, functional and symptom scores did not change or trivially changed during RT. This suggests that RT does not influence those global, functional, symptom or body image scales.

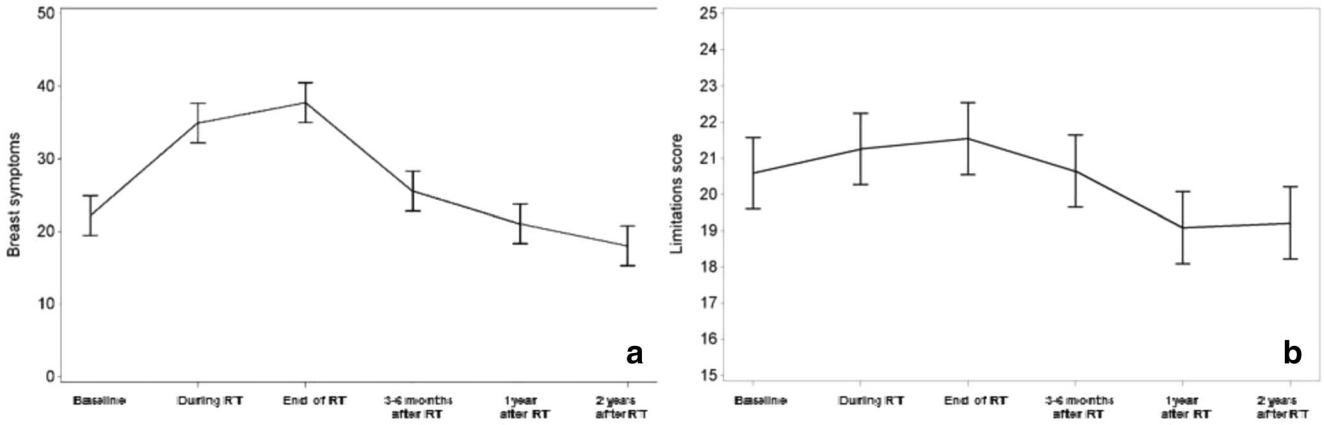

Fig. 2 Breast symptoms (**a**) and limitations (**b**) over time. Note that the *y*-axis does not show the full range of 0–100

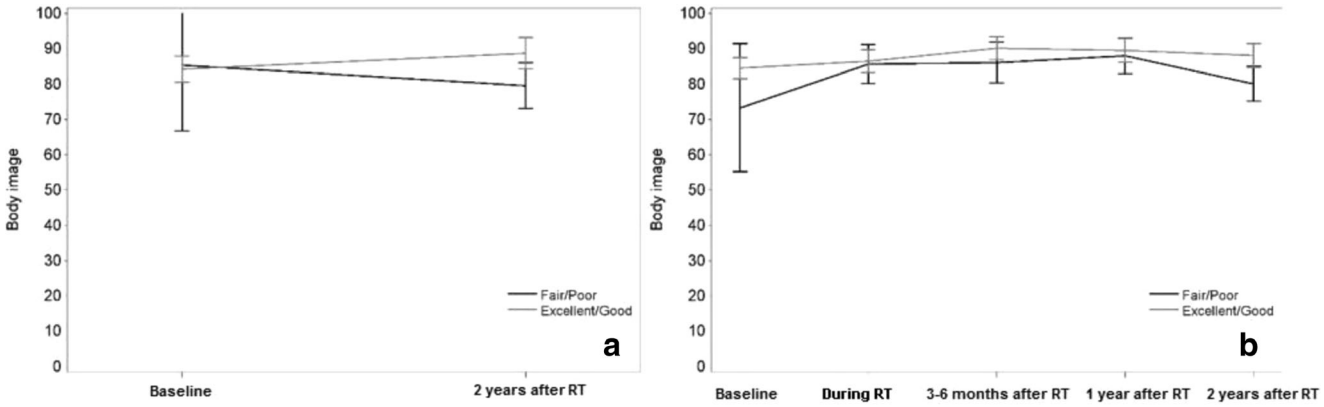

Fig. 3 Body image over time in favourable (excellent/good) and unfavourable (fair/poor) aesthetic outcome groups scored by the patient (**a**) and measured by BCCT.core (**b**)

Only for fatigue and cognitive functioning, a small deterioration was observed at the beginning of RT treatment. The initial worsening of fatigue during RT, which has been reported in older studies, thus seems to remain a current matter [32–34]. Fatigue is suggested to be determined by demographic factors rather than by cancer itself and prior cancer treatments including surgery, systemic therapy and RT [35]. Concerning the initial decrease in cognitive functioning, we believe this might at least partly be explained by initial fear or anxiety, which decreases during RT leading to lower values of the fatigue scale as well.

Besides cancer-related QOL, we have also extensively investigated changes in body image scales during the course of contemporary RT. An initial increase in breast symptoms was observed, in line with a smaller report on 75 patients [36]. Furthermore, to the best of our knowledge, we are the first to assess PROMs with the BIBCQ during RT and noticed an initial increase in limitations. These findings reflect the local effect of RT, which can produce a skin reaction and swelling of the irradiated area.

Good recovery of QOL up to 1 year and of body image up to 2 years after RT

Most unsatisfactory PROMs improved significantly up to 1 year after RT. It thus seems that these known long-term improvements are still true for contemporary techniques [30, 37]. The observed improvements over time are probably the result of several mechanisms. Firstly, a true improvement over time, with fewer physical complaints, may be present after the initial stress of diagnosis and the first treatment phase. Secondly, although controversy exists, the measurements may be influenced by a response shift [38]. This means that the basis on which people make a self-evaluation may also shift over time [30].

Global health status, future perspective, fatigue and insomnia however remained unsatisfactory. Opposite to what is generally believed, our series and others have noticed an improvement in fatigue [30, 39]. It might be possible that the common misconception of an increase in fatigue over time is due to the pertained unsatisfactory levels (symptom scores more than 20). Future studies should firstly focus on the persistent unsatisfactory fatigue looking for underlying causes and explanations. Secondly, future perspectives and global health status should further be addressed.

Another important result of the present study is that no significant changes in QOL were observed between 1 and 2 years after RT. This suggests only the 1-year time point after RT should be enough to evaluate for the global cancer-related QOL. Correlations with longer follow-up are part of this ongoing project.

Significant changes between 1 and 2 years were observed for the patient's body image. Firstly, breast symptoms, which significantly increased during RT, decreased afterwards up to 2 years after RT to lower values than at baseline and are then considered satisfactory. Friese et al. have shown an increase in skin irritation from 7 to 22% due to RT in a cross-sectional study [13]. In the randomised Cambridge breast IMRT trial, worse toxicity was also reported for the breast symptom scales at 2 months with a significant improvement over time up to 5 years after treatment [14]. Heil et al. have assessed 138 patients treated with BCT and noticed a significant improvement in breast sensitivity status (pain, tenderness and physical sensitivity) 1 year after treatment [40]. Similar patterns were also observed in older studies with outdated treatment techniques [41]. The obtained results are presumably related to unresolved acute post-RT skin changes (skin erythema and breast oedema), which are expected to improve over a period of time. Nonetheless, long term RT changes like skin telangiectasia, breast shrinkage and induration are expected to progress over time [14]. Secondly, sexual enjoyment was the only PROM that deteriorated over time; however, changes were minimal and with p value 0.06 not significant. Also, levels of sexual activity and enjoyment in the present cohort were low overall, as reported in other published data assessing breast cancer patients [42].

Good agreement within AO measurements and with specific PROMs

The second aim of the study was to explore the agreement between PROMs and AO. Around 30% of the patients had unfavourable AO 2 years after RT. AO scored by the patient and with the BCCT.core associated well with each other and with the body image measures meaning that both AO measurements are valid. Sneeuw et al. have observed similar correlations in a smaller population of 76 patients [43]. There was no association between AO and global cancer-related QOL in the present cohort. It has however been suggested that pronounced breast asymmetry after BCS significantly correlates with poor psychosocial functioning due to feelings of stigmatisation and depressive symptoms [44].

The strengths of the present study are its population-based design, longitudinal follow-up and excellent response rates, providing a representative sample of sufficient size to evaluate the patient's QOL and body image. Limitations are the heterogeneity of the group and the studies non-randomised and non-comparator design. Also, this is a monocentric study so the data cannot be generalised to other patient cohorts without comparison. Attention should thereby be given to the possible impact of sociocultural backgrounds. Furthermore, interpretations on (un)satisfactory scores are made according to the recommendations by Aaronson et al. but in reality, scores reflect a continuum from 0 to 100 and an increase from 79 to 81 for example does not necessarily mean a flip from unsatisfied to satisfied and is not the same as an increase from 50 to 81. Further studies are needed, and if study conclusions are supported, one possible clinical application would be to discuss PROMs results with patients during treatment decision-making.

In conclusion, the study suggests that quality of life and body image are temporarily impaired due to RT in the BCT setting. Around one third of patients score their long-term AO as unfavourable. These data should be discussed with the patient and could help in the decision making of the treatment plan and in the clarification of the patient's expectations.

Funding This project is realised with the support of Kom op tegen Kanker.

Compliance with ethical standards Informed consent was obtained. The study was approved by the Clinical Trial Centre and the Ethical Committee of our institution.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Ervik M et al (2014) GLOBOCAN 2012 v1.1, Cancer Incidence and. International Agency for Research on Cancer, Lyon [Cited: March 25, 2018]. http://globocan.iarc.fr
2. Desantis C, Ma J, Bryan L, Jemal A (2014) Breast cancer statistics. CA Cancer J Clinv 6:52–62
3. van Maaren M, de Munck L, de Bock G et al (2016) 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol 17:1158–1170
4. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J (2014) Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 149: 267–274
5. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233–1241
6. Litière S, Werutsky G, Fentiman IS, Rutgers E, Christiaens MR, van Limbergen E, Baaijens MHA, Bogaerts J, Bartelink H (2012) Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol 13:412–419
7. Darby S, McGale P, Correa C et al (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10, 801 women in 17 randomised trials. Lancet 378:1707–1716
8. Prescott R, Kunkler I, Williams L et al (2007) A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technol Assess 11:141–149
9. Darby SC, Ewertz M, McGale P et al (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368:387–398
10. Taylor C, Correa C, Duane F et al (2017) (EBCTCG). Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 35:1641–1649
11. Ewertz M, Jensen A (2011) Late effects of breast cancer treatment and potentials for rehabilitation. Acta Oncol 50:187–193
12. United Kingdom Department of Health (2007) Guidance on the routine colletion of patient reported outcome measures (PROMs)
13. Friese C, Harrison J, Janz N et al (2017) Treatment-associated toxicities reported by patients with early-stage invasive breast cancer. Cancer 123:1925–1934
14. Mukesh MB, Qian W, Weilkinson JS et al (2014) Patient reported outcome measures (PROMs) following forward planned field-in field IMRT: results from the Cambridge breast IMRT trial. Radiother Oncol 111:270–275
15. Al-Ghazal S, Fallowfield L, Blamey R (1999) Does cosmetic outcome from treatment of primary breast cancer influence psychosocial morbidity? Eur J Surg Oncol 25:571–573
16. Mukesh M, Qian W, Hak C et al (2016) The Cambridge breast intensity-modulated radiotherapy trial: comparison of clinican- versus patient-reported outcomes. Clin Oncol 28:354–364
17. Ganz P, Kwan L, Snanton A et al (2004) Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. J Natl Cancer Inst 96:376–387
18. Abernethy A, Etheredge L, Ganz P et al (2010) Rapid-learning system for cancer care. J Clin Oncol 28:4268–4274
19. Verhoeven K, Kindts I, Laenen A, Peeters S, Janssen H, van Limbergen E, Weltens C (2015) A comparison of three different

radiotherapy boost techniques after breast conserving therapy for breast cancer. Breast 24:391–396
20. Chen C, Cano S, Klassen A et al (2010) Measuring quality of life in oncologic breast surgery: a systematic review of patient-reported outcome measures. Breast J 16:587–597
21. Ong W, Schouwenburg M, van Bommel A et al (2017) A standard set of value-based patient-centered outcomes for breast cancer. The International Consortium for Health Outcomes Measurement (ICHOM) initiative. JAMA Oncol 3:677–685
22. Kanatas A, Velikova G, Roe B, Horgan K, Ghazali N, Shaw RJ, Rogers SN (2012) Patient-reported outcomes in breast oncology: a review of validated outcome instruments. Tumori 98:678–688
23. Aaronson N, Ahmedzai S, Bergman B et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
24. Cocks K, King M, Velikova G et al (2012) Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 48:1713–1721
25. Sprangers M, Groenvold M, Arraras J et al (1996) The European Organization for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire module: first results from a three-country field study. J Clin Oncol 14:2756–2768
26. Osaba D, Rodrigues G, Pymes J et al (1998) Interpreting the significance of changes in health-related quality of-life scores. J Clin Oncol 16:139–144
27. Baxter NN, Goodwin PJ, Mcleod RS, Dion R, Devins G, Bombardier C (2006) Reliability and validity of the body image after breast cancer questionnaire. Breast J 12:221–232
28. Harris J, Levene M, Svensson G, Hellman S (1979) Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 5: 257–261
29. Cardoso JS, Cardoso MJ (2007) Towards an intelligent medical system for the aesthetic evaluation of breast cancer conservative treatment. Artif Intell Med 40:115–126
30. Bantema-Joppe A, de Bock G, Woltman-van Iersel M et al (2015) The impact of age on changes in quality of life among breast cancer survivors treated with breast-conserving surgery and radiotherapy. Br J Cancer 112:636–643
31. Wöckel A, Schwentner L, Krockenberger M, Kreienberg R, Janni W, Wischnewsky M, Thorsten K, Felix F, Riccardo F, Blettner M, Singer S (2017) Predictors of the course of quality of life during therapy in women with primary breast cancer. Qual Life Res 26: 2201–2208
32. Budischewski K, Fischbeck S, Mose S (2008) Quality of life of breast cancer patients in the course of adjuvant radiotherapy. Support Care Cancer 16:299–304
33. Noal S, Levy C, Hardouin A, Rieux C, Heutte N, Ségura C, Collet F, Allouache D, Switsers O, Delcambre C, Delozier T, Henry-Amar M, Joly F (2011) One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. Int J Radiat Oncol Biol Phys 81:795–803
34. Lee T, Kilbreast S, Refshauge K, Pendlebury S, Beith J, Lee M (2008) Quality of life of women treated with radiotherapy for breast cancer. Support Care Cancer 16:399–405
35. Tabrizi F, Alizadeh S (2017) Cancer related fatigue in breast cancer survivors: in correlation to demographic factors. Maedica (Buchar) 12:106–111
36. Browall M, Ahlberg K, Karlsson P, Danielson E, Persson L, Gaston-Johansson F (2008) Health-related quality of life during adjuvant treatment for breast cancer among postmenopausal women. Eur J Oncol Nurs 12:180–189
37. Hsu T, Ennis M, Hood N, Graham M, Goodwin P (2013) Quality of life in long-term breast cancer survivors. J Clin Oncol 31:3540–3548
38. Visser M, Oort F, van Lanschot J et al (2013) The role of recalibration response shift in explaining bodily pain in cancer patients undergoing invasive surgery: an empirical investigation of the Sprangers and Schwartz model. Psychooncol 22:515–522
39. Goldstein D, Bennett B, Webber K et al (2012) Cancer-related fatigue in women with breast cancer: outcomes of a 5-year prospective study. J Clin Oncol 30:1805–1812
40. Heil J, Czink E, Golatta M, Schott S, Hof H, Jenetzky E, Blumenstein M, Maleika A, Rauch G, Sohn C (2011) Change of aesthetic and functional outcome over time and their relationship to quality of life after breast conserving therapy. Eur J Surg Oncol 37:116–121
41. Schmitz K, Speck R, Rye S, DiSipio T, Hayes S (2012) Prevalence of breast cancer treatment sequelae over 6 years of follow-iup: the pulling through study. Cancer 118:2217–2225
42. Rayan G, Dawson L, Bezjak A et al (2003) Prospective comparison of breast pain in patients participating in a randomized trial of breast-conserving surgery and tamoxifen with or without radiotherapy. Int J Radiat Oncol Biol Phys 55:154–161
43. Sneeuw K, Aaronson N, Yarnold J et al (1992) Cosmetic and functional outcomes of breast conserving treatment for early stage breast cancer. 2. Relationship with psychosocial functioning. Radiother Oncol 25:160–166
44. Waljee J, Hu E, Ubel P, Smith D, Newman L, Alderman A (2008) Effect of esthetic outcome after breast-conserving surgery on psychosocial functionaning and quality of life. J Clin Oncol 26:3331–3337