THE IRRADIATED BREAST

Impact on the patient and potential solutions for skin toxicity

Marilot Batenburg

The irradiated breast: impact on the patient and potential solutions for skin toxicity

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The irradiated breast: impact on the patient and potential solutions for skin toxicity

De bestraalde borst: Impact op de patiënt en mogelijke oplossingen voor toxiciteit van de huid

(met een samenvatting in het Nederlands)

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Contents

1

Introduction and thesis outline

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Breast cancer; the numbers

Breast cancer is the most common type of cancer among women (1). The lifetime risk of getting breast cancer for women in Western countries is 12-13% (2). Each year, approximately 17,000 patients are diagnosed with breast cancer in the Netherlands (3). The majority of these patients (n=10,597) is between 45-75 years of age (3). Fortunately though, new techniques have been developed and implemented, such as digital mammography, more effective systemic therapy, intensity modulated radiotherapy-techniques and hypofractionation (4–7). The current 5-year survival is 88% and 10-year survival for patients diagnosed between 2001 and 2010 was 76% (3). Consequently, the number of patients living with the consequences of breast cancer and breast cancer treatment is increasing.

Current treatment of breast cancer entails (a combination of) surgery, chemotherapy, radiotherapy, hormonal therapy, and / or HER2-targeted therapy, depending on the tumor and patient characteristics. New and less invasive techniques, such as breast conserving surgery, sentinel node procedure and 3D radiotherapy have been developed over the past decades with the aim to reduce (late) toxicity with similar survival rates (8–10).

Patient reported outcomes

The real impact of breast cancer treatment is not only measured by survival and recurrence statistics, but also by patient reported outcomes, such as physical functioning, mental functioning and quality of life. In the past decades, various questionnaires were developed and validated in order to evaluate patient reported outcomes (11,12). In addition, the International Consortium for Health Outcome Measurements (ICHOM) was developed to provide standardization for research and clinical care by proposing a selection of validated PROs on regular follow-up moments. If the guidelines of ICHOM were implemented in all longitudinal research and routine clinical care, it would be easier to compare outcomes of different treatment techniques.

In order to continuously evaluate new treatment techniques, as well as long-term outcomes after breast cancer, the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA study) was initiated

in 2013 (13). PROs within the UMBRELLA study are collected in accordance with the ICHOM guidelines. In UMBRELLA, all patients referred for radiotherapy to the UMCU or surgery in multiple hospitals in the Netherlands are asked to participate in this study. In UMBRELLA, patients may consent to use of their clinical data for research, and collection of patient reported outcomes. Patient reported outcomes, such as quality of life, physical functioning, psychosocial functioning, fatigue, cosmetic satisfaction are collected every 6 months by means of various validated questionnaires. The outcomes collected within the UMBRELLA study can be used for longitudinal studies, as seen in chapter 2 and 3 of this thesis. In addition, patients may provide broad consent for future randomization (13,14). Consequently, UMBRELLA serves as a multitrial infrastructure following the Trials within Cohorts (TwiCs) design. Here, eligible patients for a certain intervention are identified from the prospective cohort and randomized (15). Only patients randomized to the intervention group are offered the intervention, which they, in turn, may accept or refuse. Patients in the control group remain in the cohort. Outcome measures (e.g., fatigue, physical functioning, workability, cosmetic outcomes or depression) in this TwiCs design are collected within the cohort. In chapter 7, a trial protocol for a TWiCs within the UMBRELLA study is proposed. The outcomes of the observational studies as well as TWiCs within UMBRELLA can be used to inform patients about their expected quality of life during and after breast cancer treatment, as well as to improve breast cancer treatments.

Late radiation toxicity

Currently, the majority of breast cancer patients is treated with breast-conserving therapy. As a result, approximately 66% of breast cancer patients receive adjuvant radiotherapy (16). Radiotherapy plays an essential role in the prevention of breast cancer recurrence and can improve survival (17). However, radiotherapy (in combination with other breast cancer treatments) may result in late radiation toxicity. Radiotherapy may cause cardiotoxicity and pulmonary toxicity, as well as toxicity of the skin. This thesis focusses on late (local) radiation toxicity of the skin, which is characterized by a combination of pain, fibrosis, breast and / or arm edema, impaired arm movement and an impaired cosmetic outcome as from three months after radiotherapy (10,18–20). New radiotherapy techniques, such as 3D radiotherapy instead of 2D radiotherapy and lower radiotherapy doses due to hypofractionation schedules, have led to a reduction in toxicity rates over the last

decades (10,21–23). However, there is still room for improvement. It is important to identify factors associated with late radiation toxicity in breast cancer patients. Knowing these factors may be helpful to identify patients that are at risk for late radiation toxicity, as well as to inform them prior to radiotherapy and to initiate early intervention in case late radiation toxicity occurs. Furthermore, the impact of late radiation toxicity after breast cancer on quality of life is still unclear. Chapter 5 and 6 focus on late local radiation toxicity after breast cancer and the impact of late radiation toxicity on quality of life. Current treatment of late radiation toxicity mostly focusses on symptom management. Most treatments, such as analgesics and lymphedema therapy provide temporarily relief of pain or edema (24,25). Plastic surgery, such as lipofilling, may provide a more long-term solution (26,27). However, not all patients are eligible for plastic surgery, leaving a group of patients that need treatment with, for example, edema therapy.

Hyperbaric oxygen therapy

Another treatment option for late radiation toxicity is hyperbaric oxygen therapy. With hyperbaric oxygen therapy patients breath in 100% oxygen in a hyperbaric chamber with increased air pressure (i.e., 2.4 atmospheres absolute) (28–30). Hyperbaric oxygen therapy consists of 40 treatment sessions of 2 to 3 hours each, five times a week. The combination of increased pressure and 100% oxygen allows the oxygen to distribute into the damaged tissue and induces neovascularization and regeneration of the irradiated (hypoxic) tissue (31). Hyperbaric oxygen therapy is currently offered to breast cancer patients with late radiation toxicity who experience insufficient results from physiotherapy, edema therapy, analgesics and / or plastic surgery. Even though hyperbaric oxygen therapy has been proven effective as a treatment for late radiation toxicity after head and neck cancer, bladder cancer and gynecological tumors (32–34), evidence of the effectiveness in breast cancer patients is limited. Studies investigating treatment with hyperbaric oxygen therapy in breast cancer patients show mostly decrease of breast and chest wall pain (28,29). However, these studies are either small and without a control group, or suffered with patient accrual when they used a classic randomized controlled trial design. Chapter 7 and 8 focuses on treatment of late radiation toxicity with hyperbaric oxygen therapy after breast cancer treatment. Symptoms of late radiation toxicity after hyperbaric oxygen therapy are evaluated in a large cohort of breast cancer patients in chapter 7. In addition, quality of life

after hyperbaric oxygen therapy and side effects of hyperbaric oxygen therapy are evaluated. Chapter 8 describes a trial protocol in accordance with the TWiCs design (HONEY study) that will be performed within the UMBRELLA cohort.

Research objectives and outline thesis

Overall, the aim of this thesis was to evaluate quality of life after breast cancer treatment and to identify patients with a poorer quality of life. For that reason, determinants associated with poorer outcome were evaluated in several chapters. The second part of this thesis focusses on late radiation toxicity. Symptoms of late radiation toxicity were evaluated in the UMBRELLA cohort and the impact of late radiation toxicity on quality of life was assessed. In a systematic review, the determinants associated with late radiation toxicity were evaluated. Finally, treatment with hyperbaric oxygen therapy for breast cancer patients was evaluated.

Chapter 2: Evaluate patient-reported cosmetic satisfaction in women treated with radiation therapy for breast cancer and determine the association between dissatisfaction and quality of life (QoL) and depression.

Chapter 3: Evaluate to what extent breast cancer patients report poorer body image during the first four years after breast cancer treatment and to identify determinants associated with an impaired body image.

Chapter 4: Assess determinants associated with late radiation toxicity in patients treated for breast cancer.

Chapter 5: Assess the patient-reported prevalence of late radiation toxicity of the skin (LRT) in irradiated breast cancer patients and to determine the association between late radiation toxicity and different domains of quality of life.

Chapter 6: Evaluate symptoms of late radiation toxicity, side effects and quality of life in breast cancer patients treated with hyperbaric oxygen therapy (HBOT).

Chapter 7: The “Hyperbaric OxygeN therapy on brEast cancer patients with late radiation toxicity” (HONEY) trial aims to evaluate the effectiveness of HBOT on late radiation toxicity in breast cancer patients using the trial within cohorts (TwiCs) design.

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2

Patient-reported cosmetic satisfaction and the long-term association with quality of life in irradiated breast cancer patients

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Abstract

Purpose: To evaluate patient-reported cosmetic satisfaction in women treated with radiation therapy for breast cancer and to determine the association between dissatisfaction and quality of life (QoL) and depression.

Methods: Within the prospective UMBRELLA breast cancer cohort, all patients ≥ 1 year after breast conserving treatment or mastectomy with immediate reconstruction were selected. Self-reported cosmetic satisfaction was measured on a 5-point Likert scale. QoL, social and emotional functioning were measured using EORTC QLQ-C30 and BR23 at 1, 2 and 3 years after inclusion. Mixed model analysis was performed to assess the difference in different domains of QoL between patients with good versus poor self-reported cosmetic satisfaction over time after adjustment for potential confounders. Depression scores were collected by means of the HADS-NL questionnaire. Chi-square test or Fisher's exact test was used to assess the difference in proportions of HADS score ≥ 8, indicating increased depression risk, between satisfied and dissatisfied patients.

Results: 808 patients were selected for analysis. Respectively one, two, and three years after surgery, 8% (*n* = 63/808), 7% (*n* = 45/626), and 8% (*n* = 31/409) of patients were dissatisfied with their cosmetic outcome. Poor patient-reported cosmetic satisfaction was independently associated with impaired QoL, body image, and lower emotional, and social functioning. Scores ≥8 on the HADS depression subscale were significantly more common in dissatisfied patients.

Conclusions: Dissatisfaction with cosmetic outcome was low after breast cancer surgery followed by radiation therapy during 3 years follow-up. Knowing the association between dissatisfaction with cosmetic outcome and QoL and depression could help to improve the preoperative counseling of breast cancer patients.

Keywords: Breast cancer, Cosmetic outcome, Radiation therapy, Quality of life, Longitudinal

Introduction

Due to the rising incidence of breast cancer, and the improved survival rates, the number of women living with the consequences of breast cancer and breast cancer treatment is growing (1). As a result, cosmetic satisfaction and quality of life (QoL) after breast cancer treatment are increasingly being recognized as important.

Since the introduction of breast cancer screening programs, breast cancer is often detected at an earlier stage (2). Consequentially, the majority of breast cancer patients can be treated with breast-conserving therapy, a combination of breast-conserving surgery and breast irradiation (3,4). Concurrently, the interest in oncoplastic and reconstructive surgery is rising, leading to improved cosmetic results and consequently higher expectations in patients. However, the long-term degree of self-reported cosmetic satisfaction with modern treatments and how this affects QoL is yet unclear.

The aim of this study was to evaluate the prevalence of poor patient-reported cosmetic satisfaction up to 3 years following breast cancer treatment, to assess the determinants associated with poor cosmetic outcome, and to evaluate the association of poor cosmetic satisfaction with social functioning, emotional functioning, body image, and depression.

Methods

This study was conducted within the UMBRELLA cohort (Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion) (5). This prospective observational cohort includes breast cancer patients referred for post-operative radiation therapy to the department of Radiation Oncology at the Utrecht Medical Center Utrecht (UMC), the Netherlands. Here, prior to the start of radiation therapy, all breast cancer patients are invited to participate in the UMBRELLA study. Inclusion criteria are invasive breast cancer or ductal carcinoma in situ (DCIS), age over 18 years, and good understanding of the Dutch language. The UMBRELLA study complies with the Dutch law on Medical Research in Humans and was approved by the Medical Ethical Committee of the UMC.

Upon inclusion, all patients were asked for informed consent for the collection of clinical data and patient-reported outcomes (PROs). Clinical data were obtained

through the Netherlands Comprehensive Cancer Organization (IKNL) (1). Data on PROs were collected through self-reported questionnaires, which were collected before the start of radiation therapy (baseline) and at 3, 6, 12, 18, and 24 months after inclusion.

All patients enrolled in UMBRELLA between October 2013 and June 2018 were eligible for this study. Patients were selected when they completed the cosmetic evaluation questionnaire at 12 months after inclusion. In the cosmetic evaluation questionnaire the treated breast is compared to contralateral breast, therefore patients with mastectomy without breast reconstruction were excluded.

Cosmetic satisfaction was measured by means of a structured questionnaire by Sneeuw et al. (6). This questionnaire was specifically designed to measure satisfaction with the breast after radiation therapy. Patients reported their satisfaction with cosmetic outcome in comparison to the contralateral breast on a 5-point Likert scale. UMBRELLA participants filled out this questionnaire at 12 months after inclusion, as scars will have matured at this time, and again at 24 months and 36 months.

Subdomains on quality of life, emotional, and social functioning were collected with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaires and body image was collected by means of the breast cancer specific BR23 questionnaire (7). Each subscale contains a different number of items to be scored, and each individual item was scored on a 4-point Likert scale (body image, emotional functioning and social functioning) or 7-point Likert scale (global QoL). The scores for global QoL, body image, emotional functioning and social functioning were calculated using the EORTC scoring manual. Total score of one subscale ranges from 1 to 100. A higher score indicates a better outcome.

PROs on depression were collected through the Hospital Anxiety and Depression Scale (HADS, Dutch translation) questionnaire (8). HADS is a 14-item self-rating scale with seven questions to measure the symptoms of depression. Each question has four answer options, leading to a score between 0 and 3 for each question. Higher scores indicate a higher risk of depression. An increased risk of depressive disorders was defined as a HADS score $\geq$ 8. A Dutch reference population (n = 904), matched for age and gender, was used for the EORTC QLQ-C30 and HADS depression scores (9).

Clinical data including type of surgery, axillary treatment, tumor size, radiation therapy, and primary (neoadjuvant) or post-operative systemic treatment with hormonal therapy or chemotherapy were collected through the IKNL. Information on age, height, weight and smoking behavior, was collected within the UMBRELLA cohort through a bi-annual questionnaire. Age is defined as age upon inclusion. Smoking was classified as 'yes' when patients were active smokers during follow-up and 'no' for non-active smokers. Body mass index (BMI) scores were based on mean height (m) and weight (kg) during follow-up. BMI was calculated as weight/height^2.

Statistics

Patient demographics and tumor and treatment characteristics were used to compare proportions, frequencies, and means with standard deviations between three groups of patients: satisfied, neutral, or dissatisfied with cosmetic outcome. Patient, treatment and tumor characteristics of patients who responded to the cosmetic questionnaire were compared to those of patients who did not respond to the cosmetic questionnaire.

Changes in QoL, body image, emotional functioning, and social functioning between satisfied and dissatisfied patients were analyzed using a linear mixed-effect model to account for correlation between subjects over time. For mixed model analysis the self-reported cosmetic outcome was dichotomized into satisfied/neutral with cosmetic outcome and dissatisfied with cosmetic outcome. The model included a random intercept, a linear time effect, and time-cosmetic outcome interaction. We adjusted for potential confounders, i.e., age (continuous), type of surgery (lumpectomy vs. breast reconstruction), hormonal therapy, chemotherapy ± immunotherapy, BMI ($\leq$ 25 vs. $>$ 25), active smoking during follow-up, axillary treatment (sentinel node procedure vs. axillary lymph node procedure), radiation therapy (local vs. locoregional), and radiation therapy boost on the tumor bed. An autoregressive covariance structure of the first order was included, since it was assumed that measurements closer together in time were more correlated than measurements further apart (10).

Differences in proportions of high depression scores (a HADS-NL score $\geq$ 8) were compared between satisfied and dissatisfied patients, using a Chi-square test and Fisher's exact test. A p-value $<$ 0.05 was considered significant. Analyses

were performed with Statistical Package for Social Sciences software (IBM SPSS Statistics version 23).

Results

Between October 2013 and June 2018, 2140 patients were enrolled in the UMBRELLA cohort. Of those, 425 patients had a follow-up < 12 months, 292 patients had no clinical data available, 85 patients were treated with mastectomy without reconstruction, and 530 patients did not respond to the cosmetic questionnaire at 12 months (i.e., non-responders). These patients were excluded, resulting in 808 patients eligible for the present study (Figure 1). Breast cancer treatment of women who responded to cosmetic questionnaires was comparable to that of patients who did not respond to cosmetic questionnaire (Table 1). There were more missing data on QoL, smoking, and BMI in non-responders in comparison to patients included in this study (respectively 41% vs. 10% and 55% vs 7%).

The respective mean age at inclusion of satisfied, neutral, and dissatisfied patients was 58, 56, and 56 years. Of the patients satisfied at 12 months after inclusion, 97% (*n* = 569/584) was treated with breast-conserving surgery. This was respectively 91% of the neutral patients (*n* = 147/161) and 84% of dissatisfied patients (*n* = 53/63). A larger proportion of dissatisfied patients was treated with chemotherapy in contrast to neutral and satisfied patients (respectively 51%, 45%, and 30%) as well as hormonal therapy (respectively 54%, 53%, and 43%). Also, 16% of the dissatisfied patients was treated with locoregional radiation therapy in contrast to 14% of the neutral and 7% of the satisfied patients. The proportion of satisfied, neutral, and dissatisfied patients was approximately equally distributed for radiation therapy boost, active smoking, and body mass index (respectively 49-52%, 10-12% and 48-60%).

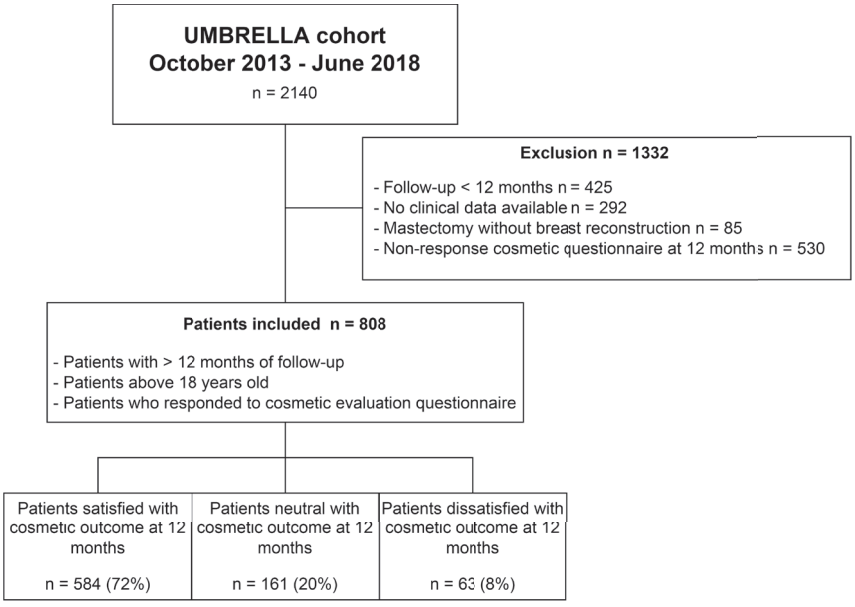
Dissatisfied patients had lower levels of unadjusted QoL body image, and social and emotional functioning compared to patients satisfied with cosmetic outcome (Figure 2). Satisfied patients reported higher scores of global QoL in comparison to the reference population at all time-points. Social and emotional functioning of satisfied patients was comparable to that of the Dutch reference population. In contrast, dissatisfied patients reported poorer social and emotional functioning compared to the Dutch reference population during follow-up.

Table 1. Patient and treatment characteristics of patients who responded to the cosmetic questionnaire vs. non-responders to cosmetic questionnaire.

	Included in study *n* = 808	**Non-responders** *n* = 530
Age (mean (SD))	58 (10)	57 (12)
Tumor size in mm (mean (SD))	15 (12)	16 (13)
Unknown (*n* (%))	51 (6)	21 (4)
Type of surgery		
Breast conserving surgery	769 (95)	493 (93)
Mastectomy combined with breast reconstruction	39 (5)	37 (7)
Axillary treatment [a]		
Axillary lymph node dissection	67 (8)	44 (8)
Sentinel node procedure	682 (84)	437 (82)
Unknown	59 (7)	49 (9)
Chemotherapy [b]		
Yes	278 (34)	191 (36)
No	530 (66)	339 (64)
Hormonal treatment [b]		
Yes	372 (46)	249 (47)
No	436 (54)	281 (53)
Type of radiation therapy		
Local	720 (89)	408 (77)
Locoregional[c]	74 (9)	117 (22)
Unknown	14 (2)	5 (1)
Radiation therapy boost [a]		
Yes	384 (48)	263 (50)
No	410 (51)	264 (50)
Unknown	14 (2)	3 (1)
Smoking		
Yes	84 (10)	42 (8)
No	669 (83)	196 (37)
Unknown	55 (7)	292 (55)
Body mass index [a,d]		
BMI ≤ 25	343 (43)	106 (20)
BMI > 25	410 (51)	132 (25)
Unknown/not reported	55 (7)	292 (55)
Quality of life at enrolment (mean (SD))[e]	74 (18)	73 (18)
Unknown (*n* (%))	79 (10)	217 (41)

Unless stated otherwise, numbers are shown as *n* (%) [a] Total percentage other than 100% due to rounding; [b] Both primary systemic treatment and post-operative systemic treatment; [c] Including radiation therapy on periclavicular and/or axillary lymph nodes; [d] Calculated as weight/height^2; [e] Assessed by EORTC QLQ-C30 questionnaires, a higher score indicates better quality of life (range 0-100).

Figure. 1 Flowchart of inclusion selected patients included in the UMBRELLA study.



At 12 months, the proportion of satisfied, neutral, and dissatisfied patients was 72% (*n* = 584), 20% (*n* = 161) and 8% (*n* = 63), respectively (Table 2). The proportion of satisfied, neutral, and dissatisfied patients remained approximately stable over time. This proportion of dissatisfied patients was 8% (*n* = 63/808), 7% (*n* = 45/626) and 8% (*n* = 31/409) after 1, 2, and 3 years of follow-up respectively (Table 3). Of the patients dissatisfied with cosmetic outcome at 24 months, 60% (*n* = 27/45) was also dissatisfied at 12 months, whereas 40% (*n* = 18/45) of patients who were previously satisfied with cosmetic outcome now were dissatisfied. At 36 months, 55% (*n* = 17/31) patients were dissatisfied both at 12 months as well as at 36 months after inclusion.

Table 2. Baseline table: patient demographics, tumor specifics, and treatment specifics in relation to patient (dis)satisfaction with cosmetic outcome.

	Satisfaction with cosmetic outcome [a]		
	Satisfied *n*= 584	Neutral *n* = 161	Dissatisfied *n* = 63
Age (mean (SD))	58 (10)	56 (10)	56 (10)
Tumor size in mm (mean(SD))	14 (10)	16 (10)	19 (20)
Unknown (*n* (%))	38 (7)	11 (7)	4 (6)
Type of surgery			
Breast conserving surgery	569 (97)	147 (91)	53 (84)
Mastectomy combined with breast reconstruction [b]	15 (3)	14 (9)	10 (16)
Axillary treatment			
Axillary lymph node dissection	38 (7)	19 (11)	10 (16)
Sentinel node procedure	499 (85)	130 (81)	53 (84)
Unknown	47 (8)	12 (7)	0 (0)
Chemotherapy [c,d]			
Yes	174 (30)	72 (45)	32 (51)
No	410 (70)	89 (55)	31 (50)
Hormonal treatment [d]			
Yes	252 (43)	86 (53)	34 (54)
No	332 (57)	75 (47)	29 (46)
Type of radiation therapy			
Local	538 (92)	131 (81)	51 (81)
Locoregional [e]	42 (7)	22 (14)	10 (16)
Unknown	4 (1)	8 (5)	2 (3)
Radiation therapy boost			
Yes	276 (47)	78 (48)	30 (48)
No	304 (52)	75 (47)	31 (49)
Unknown	4 (1)	8 (5)	2 (3)
Smoking [c]			
Yes	58 (10)	20 (12)	6 (10)
No	487 (83)	130 (81)	52 (83)
Unknown	39 (7)	11 (7)	5 (8)
Body mass index [f]			
BMI ≥ 25	251 (43)	72 (45)	20 (32)
BMI > 25	294 (50)	78 (48)	38 (60)
Unknown	39 (7)	11 (7)	5 (8)

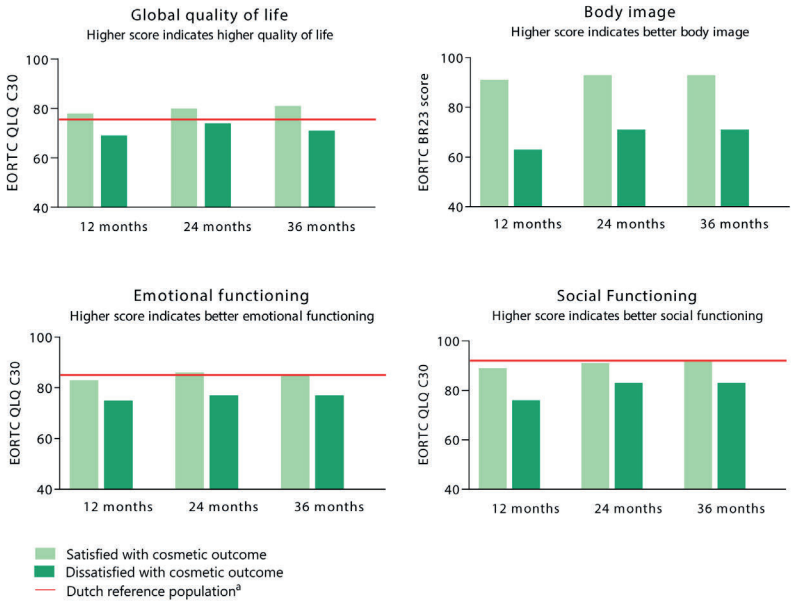
Unless stated otherwise, numbers are shown as *n* (%)
[a] Defined as satisfaction with cosmetic outcome 12 months after inclusion. [b] All breast reconstructions were performed directly after mastectomy; [c] Total percentage other than 100% due to rounding; [d] Both primary systemic treatment and post-operative systemic treatment; [e] Including radiation therapy on periclavicular and/or axillary lymph nodes; [f] Calculated as weight/height^2.

Table 3. Proportion of patients satisfied, neutral, and dissatisfied with cosmetic outcome during 3 years follow-up.

	Satisfaction with cosmetic outcome		
	Satisfied (%)	Neutral (%)	Dissatisfied (%)
1 year follow-up	584 (72)	161 (20)	63 (8)
2 years follow-up	475 (76)	106 (17)	45 (7)
3 years follow-up	305 (75)	73 (9)	31 (8)

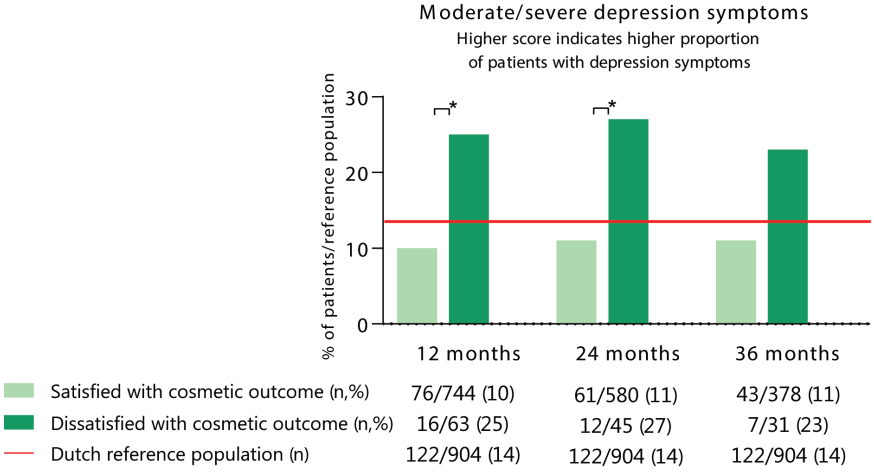
After adjustment for potential confounders (i.e., age, type of surgery, chemotherapy, hormonal therapy, BMI, smoking, axillary treatment, and radiation therapy ± boost), dissatisfied patients reported significantly lower QoL at 12 and 36 months (mean difference (MD) 6.9, 95% CI 2.1-11.6 and MD 8.8, and 95% CI 2.7-15.0) (Table 4). After 24 months, QoL was lower in dissatisfied than satisfied patients, however this difference was not significant (MD 3.4, 95% CI -1.9-8.7). Dissatisfied patients had a worse body image compared to satisfied patients at 12, 24, and 36 months (MD 22.2, 95% CI 18.1-26.4; MD 20.6, 95% CI 16.0-25.1; and MD 20.3, 95% CI 15.6-25.0) (Table 4). Also, dissatisfied patients reported lower emotional functioning at 12, 24, and 36 months in comparison to satisfied patients (respectively MD 6.8, 95% CI 1.7-12.0; MD 7.9, 95% CI 2.3-13.5; and MD 8.2, 95% CI 1.2-15.3). Social functioning of dissatisfied patients in comparison to satisfied patients was significantly lower at 12 and 36 months (MD 8.4, 95% CI 3.3-13.5; MD 6.3, 95% CI 0.1-12.2). Although not statistically significant, social functioning of dissatisfied patients was lower in comparison to satisfied patients at 24 months (MD 5.4, 95% CI -0.3-10.8). There was a significantly lower proportion of patients with symptoms suggestive of possible depression (i.e., with a HADS-NL score $\geq$8) among satisfied patients in comparison to dissatisfied patients after 12 and 24 months of follow-up (respectively 10% vs. 25% and 11% vs. 27%), in contrast to 14% in the Dutch reference population (Figure 3). This was respectively 11% and 23% after 36 months of follow-up (not statistically significant).

Figure. 2 The crude levels of different domains of QoL in respect to cosmetic outcome and a matched Dutch reference non-cancer population[a].



[a] A reference population for quality of life, emotional functioning, and social functioning was available. There is currently no reference population available for body image. Reference population included 907 women without breast cancer with comparable age to study population.

Figure. 3 Proportion of dissatisfied and satisfied patients with a HADS-NL depression score ≥ 8 after 12, 24, and 36 months of follow-up.



* Significant difference of *p*-value < 0.05 based on Chi-square test at 12 and 24 months and Fisher's exact test at 36 months of follow-up.

Table 4. Results of mixed model analysis with patient-reported outcome scores for patients satisfied and dissatisfied with cosmetic outcome after 12 months, 24 months, and 36 months.

	Group	12 months			24 months			36 months		
			Between group difference			Between group difference			Between group difference	
		Mean	MD	95%CI	Mean	MD	95%CI	Mean	MD	95%CI
QoL	Satisfied	78.2	Ref. group		79.6	Ref. group		80.9	Ref. group	
	Dissatisfied	71.3	6.9*	2.1- 11.6	76.2	3.4	-1.9-8.7	72.1	8.8*	2.7-15.0
Body	Satisfied	91.1	Ref. group		92.3	Ref. group		93.0	Ref. group	
image	Dissatisfied	68.9	22.2*	18.1-26.4	71.7	20.6*	16.0-25.1	72.7	20.3*	15.6-25.0
Emotional	Satisfied	83.6	Ref. group		85.7	Ref. group		85.1	Ref. group	
	Dissatisfied	76.8	6.8*	1.7-12.0	77.8	7.9*	2.3-13.5	76.9	8.2*	1.2-15.3
Social	Satisfied	88.5	Ref. group		90.8	Ref. group		91.5	Ref. group	
	Dissatisfied	80.0	8.4*	3.3-13.5	85.5	5.4	-0.3-10.8	85.2	6.3*	0.1-12.2

EORTC QLQ C30 and BR23 range from 0 to 100. A higher score indicates a better outcome. Mean scores were adjusted for age, type of surgery, chemotherapy, hormonal therapy, BMI, smoking, axillary treatment, radiation therapy, and boost.
MD: mean difference, i.e., difference in mean scores between patients dissatisfied and satisfied with cosmetic outcome.
95% CI: 95% confidence interval, Ref. group: reference group
* Significant difference with a *p*-value < 0.05

Discussion

This prospective observational study showed that a stable proportion of 7-8% of breast cancer patients treated with breast-conserving treatment or mastectomy with immediate reconstruction were dissatisfied with respect to their cosmetic outcome up until 3 years after breast cancer treatment. Cosmetic dissatisfaction was independently associated with poorer global quality of life, body image, social functioning and emotional functioning and a higher proportion of patients with moderate/severe depression scores.

Several other studies have described patient-reported cosmetic outcome after breast cancer treatment. In these studies 8-20% of the patients were dissatisfied with their cosmetic outcome (11–13). In the prospective trial of Garsa et al., 151 early-stage breast cancer patients treated with breast-conserving surgery and partial breast radiation therapy were included. The percentage of patients reporting excellent/good cosmetic outcome after respectively 3 months, 2, and 3 years after radiation therapy was 91%, 87%, and 92% (11). Garsa et al. defined patient-reported cosmetic outcome as a combination of factors (i.e., breast size, nipple/areola location and shape, appearance of the surgical scar, breast shape, and skin color). In an older prospective study of Matory et al., 57 patients were treated with as they described partial mastectomy, and most of them also with radiation therapy (12). Cosmetic outcome was assessed by physical and photographic examination using a 4-point Likert scale with "no difference from contralateral breast," "minimal difference from contralateral breast," "moderate asymmetry," and "gross distortion or asymmetry," representing respectively excellent, good, fair, and poor results. A good or excellent cosmetic result was reported by 80% (n = 50/57) of the patients after a median follow-up of 36 months, which was lower than the 93% which we found 3 years after treatment. This could be due to the fact that patients were treated with partial mastectomy. During a partial mastectomy larger tissue volume is removed in comparison to the breast-conserving surgery which is mostly performed nowadays. This can affect cosmetic outcome (14).

In accordance with the literature, we observed that younger patients were more likely to be dissatisfied with cosmetic outcome (15–18). This might be because younger patients are more likely to receive mastectomy followed by reconstruction, resulting in a greater risk of dissatisfaction (15). Another explanation may be that

younger women are more demanding and sensitive regarding their physical appearance (16–18). The use of tamoxifen is associated with the development of fibrosis, which might induce poorer cosmetic outcome (19,20). In the present study, hormonal treatment was observed more frequently in patients dissatisfied with cosmetic outcome than satisfied patients with cosmetic outcome. However, no distinction between the type of hormonal therapy was made, since data on type of hormonal therapy was often unknown. We found that axillary lymph node dissection impacted the cosmetic outcome which has been described previously. It is known that extensive axillary treatment like axillary lymph node dissection can be associated with the risk of developing lymphedema and therefore can influence the healing of the breast tissue after surgery and radiation therapy (21–23). Results of this study also indicated that more extensive radiation therapy (i.e., locoregional radiation therapy) and type of surgery (i.e., mastectomy with immediate reconstruction) impair cosmetic outcome. Other studies showed that satisfaction with cosmetic outcome in patients treated with breast-conserving therapy depends on the amount of tissue excised during surgery, with a larger amount of tissue excised resulting in a lower level of satisfaction (14,19,24–27). The higher proportion of dissatisfied patients in comparison to the neutral and satisfied patients treated with locoregional radiation therapy could be explained by the increased risk of fibrosis due to radiation therapy of the breast tissue even years after the start of radiation therapy, as the administration of an additional radiation therapy boost was distributed equally in local and locoregional treated patients (19,28–32). In the "boost vs. no boost" trial, 5318 early-stage breast cancer patients were randomized to additional boost on the tumor bed or no further treatment (19). An independent association between radiation therapy boost and poorer cosmetic outcome was seen after 3 years follow-up. In our study, the proportion of patients treated with radiation therapy boost was approximately equally distributed amongst the satisfied, neutral, and satisfied patients. However, this was only evaluated at 1 year follow-up. Breast and chest wall fibrosis develop over the course of many years and our cohort may not be mature enough to assess the impact of radiation therapy boost. In contrast to other studies, smoking and BMI had no influence on cosmetic outcome in the present study.

We aimed to assess the impact of cosmetic (dis)satisfaction on the different domains of quality of life and found a strong association between the two. Since self-reported cosmetic outcome and quality of life and depression scores were

measured simultaneously, we do not know the direction of the association. It could be that dissatisfaction with cosmetic outcome causes higher depression scores and lower quality of life. However, the contrary - higher depression scores or lower quality of life causing dissatisfaction with cosmetic outcome – may also be the case.

Previously, only the impact of cosmetic outcome on global quality of life or body image was assessed. Hau et al. evaluated the association between global quality of life and cosmetic outcome in 688 breast cancer patients treated with post-operative radiation therapy after breast-conserving surgery, using the EORTC QLQ-C30 (33). Patient-reported cosmetic outcome was dichotomized into good/excellent vs. fair/poor. Prior to radiation therapy, at 5 and 10 years follow-up, patients dissatisfied with cosmetic outcome reported a significantly lower global QoL score than satisfied patients (differences of 6.3, 9.6, and 7.3 points respectively on the EORTC QLQ-C30). These results are comparable with our results.

After adjustment for patient and treatment related factors, patients satisfied with cosmetic outcome had similar emotional, and social functioning in comparison to a Dutch reference non-cancer, female population during 3 years follow-up. Also, a smaller proportion of satisfied patients reported higher HADS scores in comparison to the Dutch reference population. Dissatisfied patients however, scored worse on all domains. Dissatisfaction with cosmetic appearance could be influenced by expectations of the cosmetic result after surgery (34,35). Therefore, managing patients' expectations and providing information about cosmetic results of patients with similar characteristics and expectations seems important, possibly by early referral to a plastic surgeon.

Our study suffers from some limitations. There were 530 patients who did not respond to the cosmetic questionnaire. Even though there were no differences in patient and treatment characteristics, we may have over- or underestimated the proportion of dissatisfied participants. Also, we cannot rule out that the association between cosmetic outcome and quality of life was distorted: it may, for example, have been stronger, when cosmetically dissatisfied women with (very) low quality of life scores were more likely to be non-responders. In the present study, smoking was defined as active smoking during follow-up. Information on the number of pack years and the start date of smoking was not available. Therefore, the impact these factors could have had on the cosmetic outcome, could not be

taken into account. Breast size prior to surgery, post-operative complications such as infection and seroma, and tumor localization within the breast are known to be risk factors for poor cosmetic outcome (13,15,22,36). These patient characteristics were not collected within the cohort. Also, the cosmetic evaluation questionnaire was only sent to patients 12, 24, and 36 months after inclusion. Consequently, we miss information on the satisfaction with cosmetic outcome shortly after surgery or prior to breast cancer treatment.

Nonetheless, this study provides insights into the longitudinal patient satisfaction with cosmetics after breast cancer and breast cancer treatment. Outcomes from this study emphasizes the importance of post-treatment care of breast cancer patients and shared decision making prior to breast cancer treatment.

Conclusion

In conclusion, dissatisfaction with cosmetic outcome in the first 3 years after breast surgery and post-operative radiation therapy is low, i.e., 7-8%. As cosmetic outcome was associated with reduced quality of life, poorer body image, reduced social and emotional functioning, and increased depressive symptom scores, counseling on the impact of satisfaction with cosmetic outcome on the quality of life could be considered.

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3

Body image in women irradiated for breast cancer after breast cancer surgery

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Submitted

Abstract

Purpose: Evaluate to what extent breast cancer patients report poorer body image during four years after breast cancer treatment and to identify determinants associated with impaired body image.

Methods: In a prospective cohort study, female breast cancer patients with ≥ 1 year follow-up after radiotherapy, who responded to baseline and ≥ 1 follow-up questionnaire were included. Body image was assessed with four items (4-point Likert scale) of the EORTC QLQ-BR23 questionnaire at baseline (after surgery and before radiotherapy) and at 3, 6, and every 6 months thereafter. Determinants independently and significantly associated with an impaired body image (i.e., 3-4 score on any item) at one year follow-up were identified with multivariable logistic regression.

Results: In total 2051 women were included. The proportion of women reporting grade 3-4 impairment on any of the body image items was 6-11% at baseline, 5-9% at 12 months and 4-6% at 48 months follow-up. The proportion with impairment was 1-3% higher at 3 months for all items compared to baseline. Undergoing chemotherapy, higher baseline body mass index, poorer baseline body image and baseline emotional functioning were independently associated with an impaired body image at follow up. Type of surgery was only associated with impaired body image in the subgroup of patients treated without chemotherapy.

Conclusion: The number of breast cancer patients experiencing impaired body image was very low.

Impact on cancer survivors: Women treated with chemotherapy, higher baseline body mass index, poorer baseline body image and poorer emotional functioning were more likely to report impaired body image.

Keywords: breast cancer, body image, quality of life, patient reported outcomes

Introduction

Women treated for breast cancer often experience physical, psychosocial and sexual problems that may persist or increase over time (1–3). The multimodality treatment may lead to physical changes, including the loss of breast(s) or breast tissue, hair loss, changes in weight or other side effects. These changes may affect the body image of women treated for breast cancer (4–6). This has resulted in women reporting to feel deformed, less feminine and less sexually attractive, which consequently may negatively affect quality of life (QoL) (5,6).

The wide variation in the use of different definitions and measurement methods of body image has resulted in a wide range of reported severity and frequency of impaired body image, such as the body image scale, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ), or self-developed questionnaires (4,6–9). Only a few of those studies have evaluated body image beyond the primary treatment of the disease (7,8,10). Therefore, the aim of this study was to evaluate the level of satisfaction with body image over the course of four years. In addition, we identified factors associated with poor body image one year after radiotherapy in women treated for breast cancer.

Methods

Participants

This study was conducted within the prospective Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA) (11). In the UMBRELLA study, patients with histologically proven invasive breast cancer or Ductal Carcinoma In Situ (DCIS) who were referred to the Department of Radiation Oncology of the University Medical Center (UMC) Utrecht for adjuvant radiotherapy (i.e., after breast cancer surgery) were included. The UMBRELLA study started in October 2013 and enrolment is still ongoing. Patients < 18 years old or patients who are unable to understand the Dutch language were excluded from cohort participation. All participants gave informed consent for collection of their clinical data and measurement of Patient Reported Outcome Measures (PROMs) at regular time intervals. The UMBRELLA study was approved by the Medical Ethical Committee of the UMC Utrecht, the Netherlands. The UMBRELLA study was published under NCT02839863 on ClinicalTrials.gov.

For the present study, female patients with a minimal follow-up of 1 year (i.e., inclusion between 2013 – August 2019) were selected. Patients who did not complete baseline PROMs or did not fill out any of the follow-up PROMs were excluded.

Data collection

Patient, tumor, and treatment characteristics were collected through the Netherlands Cancer Registry of the Netherlands Comprehensive Cancer Organization (IKNL). Age was defined as age at cohort enrolment. Weight, height, and education were collected in the context of the cohort study, and Body Mass Index (BMI) was subsequently calculated as weight / height^2. The highest reported level of education was used and subsequently dichotomized into "no schooling completed, secondary or vocational education" and "college, graduate or professional degree". Bilateral surgery was defined as breast cancer surgery performed due to previous or current breast cancer in the contralateral breast. Tumor and treatment characteristics of the most advanced / severe tumor were used for women with bilateral breast cancer.

PROMs were collected at baseline (i.e., after surgery (with or without neoadjuvant systemic treatment) and prior to radiotherapy), 3 months, 6 months and every 6 months thereafter. As patients were included prior to radiotherapy, baseline measurement was after breast cancer surgery. Body image was collected by means of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module (EORTC QLQ BR23) (12). The EORTC QLQ BR23 body image scale is based on 4 items: "Have you felt physically less attractive as a result of your disease or treatment?"; "Have you been feeling less feminine as a result of your disease or treatment?"; "Did you find it difficult to look at yourself naked?"; and "Have you been dissatisfied with your body?". All items were scored on a 4-point Likert scale (i.e., "not at all", "a little", "quite a bit", or "very much").

Physical functioning and emotional functioning were assessed with the EORTC QLQ C30 questionnaire (13). Sum scores were linearly transformed into a sum score ranging from 0 to 100 using the EORTC scoring manual (14). A higher score indicates a better outcome. The 14-item Hospital Anxiety and Depression Scale (HADS) questionnaire was used to measure self-reported anxiety and depression

(15). HADS comprises 7 items on depression on a 4-point Likert scale. A sum score ≥ 8 indicates an increased risk of depressive disorders. The HADS questionnaire was included at every time point except at 3 months after inclusion (15).

Statistical analysis

Proportions and frequencies were used for baseline categorical data. Means and standard deviations (SD) were used to describe normally distributed continuous outcomes. Otherwise medians with interquartile ranges (IQR) were used.

To evaluate which baseline determinants were associated with poorer body image one year after inclusion, body image scores were dichotomized into normal versus impaired body image. Since no threshold for a minimal clinical important difference or a clinically relevant threshold was available, participants were classified as "poor" when they answered "quite a bit" or "very much" (i.e., 3 or 4 on a 4-point Likert scale) for at least one item in the body image scale. Consequently, "normal" body image was defined as a score of 1 ("not at all") or 2 ("a little") on all body image items.

Missing clinical and patient reported baseline values were considered missing at random and were imputed using Multivariate Imputation by Chained Equations (5 imputed datasets, 10 iterations for each imputation) (16). Patient (age, educational level, BMI), treatment (type of surgery, axillary surgery, type of radiotherapy, chemotherapy, endocrine therapy) and tumor characteristics (bilateral tumor, tumor stage), as well as patient reported baseline depression, body image, physical, and emotional functioning and body image at 12 months were used as predictor variables for imputation (17). Distributions of original and imputed data were compared using stripplots. Convergence plots were used to check imputed data for convergence (i.e., if the number of iterations in the model is sufficient). Intermingling lines without any pattern were considered successful (18). Univariable and multivariable logistic regression was performed to determine which determinants were associated with poor body image. Backward stepwise selection, based on the likelihood ratio, was performed for multivariable logistic regression analysis. Potential determinants for poorer body image in breast cancer patients included: age at cohort enrolment inclusion (continuous), educational level (high / low), BMI (continuous), type of surgery (breast conserving surgery / mastectomy without reconstruction/breast reconstruction), type of axillary

surgery (axillary lymph node dissection / sentinel node procedure), bilateral breast surgery (yes / no), type of radiotherapy (local / locoregional), chemotherapy (yes / no), endocrine therapy (yes / no), and patient reported body image (continuous), physical (continuous), and emotional functioning (continuous) at baseline and baseline depression scores (≥ 8 / < 8). To avoid multicollinearity, correlations between variables were checked prior to model building. Also, model estimates were checked during model building. Both complete case analysis and analysis of imputed data were performed. Pooled estimates of coefficients were obtained using Rubin's rules (18). Odds radios (OR) with corresponding 95% confidence intervals (CI) were calculated. Statistical analyses were performed using SPSS Statistics (version 25.0) and R Studio open-source software (version 1.2.5001) with "mice", "naniar", "foreign", "tableone","lattice", and "broom"packages (http://www.R-project.org).

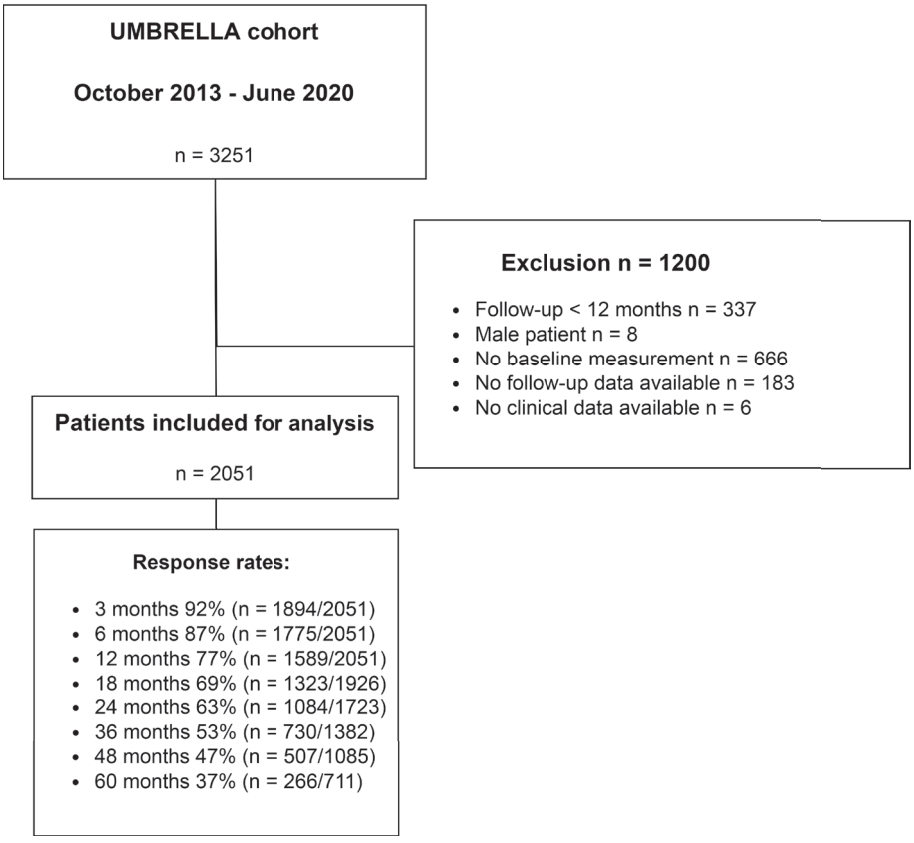
Results

Of the 3251 patients that were enrolled in the UMBRELLA study between October 2013 and August 2020, 2051 (67%) were included in the present study (Figure 1). Most patients were excluded because of non-response to the baseline questionnaire (*n* = 666, 20%) or follow-up < 12 months (*n* = 337, 10%). PROM response rates decreased from 92% at 3 months follow-up to 47% after 4 years follow-up. There was no difference in clinical characteristics and PROMs at baseline between patients who responded to questionnaires and non-responders (Supplementary table 1). The mean age at cohort enrolment was 58 years (range 20-94) (Table 1). Most patients (82%, *n* = 1684) were treated with breast conserving surgery, 39% of the patients (*n* = 803) were treated with (neo)adjuvant chemotherapy and 47% (*n* = 974) of the patients received (neo)adjuvant endocrine therapy. The median body mass index was 25.5 kg / m^2.

The proportion of patients who reported to feel "quite a bit" or "very much" less attractive as a result of treatment or disease at baseline was 10.9% (*n* = 220/2020), which decreased to 4.4% (*n* = 22/497) after 4 years follow-up (Figure 2). The proportion of patients that felt "quite a bit" or "very much" less attractive as a result of treatment or disease was the highest at 3 months follow-up (13.4%, *n* = 250/1871). The proportion of patients that felt "quite a bit" or "very much" less feminine as a result of disease or treatment was highest at 3 months after

inclusion (10.1%, *n* = 190/1872) and decreased to 4.6% (*n* = 61/1312) at 18 months. Afterwards, the proportions remained stable until 48 months follow-up. The proportion of patients that experienced "quite a bit" or "a lot of" difficulty looking at themselves naked was stable over time and ranged from 3-6%.

Figure 1. Flowchart of patients in the UMBRELLA cohort included for present study.



* Total number of patients decreases while follow-up increases, as the UMBRELLA study is a dynamic cohort and enrollment is ongoing

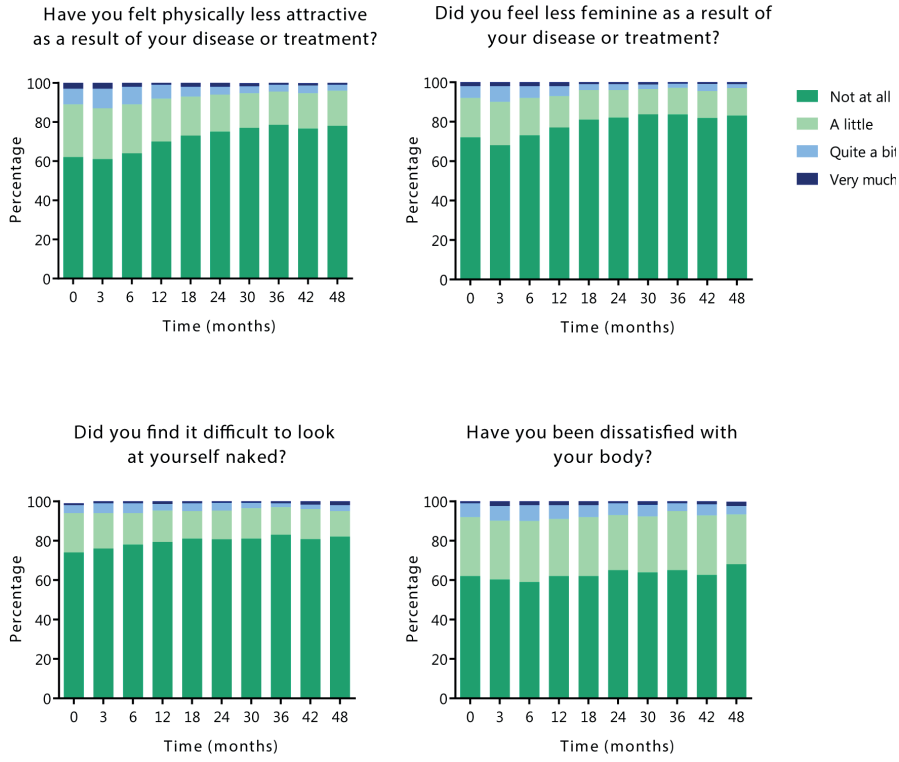
For the item "Have you been dissatisfied with your body?" the proportion of patients that were "very much" or "quite a bit" dissatisfied was 8% (*n* = 163/2018) at baseline and increased to 10% (*n* = 174/1681) after 6 months follow-up. Over time, this proportion steadily decreased to 6% (*n* = 32/496) after 4 years follow-up. Body image sum scores improved from 85.8 at baseline to 91.1 at 60 months follow-up (Supplementary figure 1).

Table 1. Patient-, tumor- and treatment characteristics of female breast cancer patients.

	n = 2051
Age at inclusion (mean (range))	58 (24-90)
Pathological tumor stage[a]	
0	339 (17)
1	1194 (58)
2	404 (20)
3	54 (3)
4	3 (<0.01)
Unknown	57 (3)
Type of surgery	
Breast conserving surgery	1684 (82)
Mastectomy without breast reconstruction	205 (10)
Mastectomy with breast reconstruction	148 (7)
Unknown	13 (0.6)
Axillary surgery	
Axillary lymph node dissection	196 (10)
Sentinel Node Procedure	1670 (81)
No axillary treatment	157 (8)
Unknown	28 (1)
Bilateral breast surgery[b]	160 (8)
Systemic treatment[c]	
Chemotherapy [d]	803 (39)
Hormonal therapy	974 (47)
Targeted therapy	220 (10)
No adjuvant treatment	826 (40)
Type of radiation therapy[a]	
Local without boost	808 (39)
Local with boost	616 (30)
Locoregional without boost [e]	270 (13)
Locoregional with boost [e]	183 (9)
Partial breast irradiation	21 (1)
Unknown	153 (8)
Body Mass Index (median (IQR)) [f]	25.5 (5.8)
Unknown	117 (6)

Numbers are shown as *n* (%) unless stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and median (IQR) otherwise.
[a] Total percentage other than 100% due to rounding. [b] Bilateral breast cancer or previous contralateral breast cancer. [c] Total percentage > 100% as patients may receive a combination of systemic treatment. [d] Both neoadjuvant as well as adjuvant chemotherapy. Some patients were also treated with immunotherapy. [e] Radiation therapy on periclavicular and / or axillary lymph nodes. [f] Weight / height^2.

Figure 2. Outcome of single items of EORTC QLQ-BR23 body image on a 4-point Likert scale.



Body image scores were available for 1561 (75%) patients at 12 months follow-up. Overall, 211 of those 1561 patients (14%) reported poor body image (i.e., 3 or 4 on 4-point Likert scale) on at least one of the four items of body image. After multiple imputation, baseline characteristics were comparable for the crude and imputed dataset (Supplementary table 2). In univariable analysis all variables with exception of bilateral breast surgery were significantly associated with poorer body image (Table 2). After backward selection, the final multivariable logistic regression model included the following factors: type of surgery, chemotherapy, body mass index, emotional functioning, depression scores and type of radiotherapy. Chemotherapy (OR 1.82, 95% CI 1.27-2.60), higher BMI (OR 1.06, 95% CI 1.03-1.09), lower baseline body image (OR 0.97, 95% CI 0.96-0.97), and lower baseline emotional functioning (OR 0.98, 95% CI 0.97-0.99) were significantly associated with impaired body image (Table 2).

Table 2. Results of multivariable logistic regression analysis after multiple imputation assessing baseline determinants associated with decreased body image at one year after inclusion.

	Univariable analysis	**Multivariable analysis**	
		Full model	**Final model**
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, per year	0.96 (0.94-0.97)*	0.99 (0.97-1.01)	
Type of surgery			
Breast conserving surgery	Ref.	Ref.	Ref.
Mastectomy without breast reconstruction	2.24 (1.45-3.37)*	1.32 (0.75-2.30)	1.23 (0.73-2.03)
Breast reconstruction	3.71 (2.40-5.67)*	1.51 (0.87-2.56)	1.66 (0.98-2.77)
Type of axillary surgery			
No axillary surgery	Ref.	Ref.	
Sentinel node procedure	2.01 (1.06-4.29)*	0.98 (0.48-2.25)	
Axillary lymph node dissection	3.50 (1.68-8.00)*	0.86 (0.35-2.25)	
Hormonal therapy			
No	Ref.	Ref.	
Yes	1.66 (1.24-2.24)*	1.15 (0.79-1.68)	
Chemotherapy [a]			
No	Ref.	Ref.	Ref.
Yes	2.50 (1.86-3.37)*	1.69 (1.12-2.57)*	1.87 (1.30-2.67)*
Body mass index	1.05 (1.03-1.08)*	1.06 (1.03-1.09)*	1.06 (1.03-1.09)*
Baseline body image [b]	0.96 (0.94-0.96)*	0.97 (0.96-0.98)*	0.97 (0.96-0.97)*
Baseline emotional functioning [b]	0.97 (0.96-0.97)*	0.98 (0.97-0.99)*	0.98 (0.97-0.99)*
Baseline physical functioning [b]	0.97 (0.97-0.98)*	0.99 (0.98-1.00)*	
Baseline depression scores [c]			
≤8	Ref.	Ref.	Ref.
>8	3.84 (2.69-5.46)*	1.40 (0.86-2.24)	1.47 (0.92-2.32)
Type of radiotherapy			
Local radiotherapy [d]	Ref.	Ref.	Ref.
Locoregional radiotherapy [e]	2.29 (1.68-3.10)*	1.06 (0.71-1.59)	1.11 (0.75-1.64)
Bilateral breast surgery			
No	Ref.	Ref.	
Yes	1.19 (0.70-1.92)	1.07 (0.58-1.88)	

After backwards stepwise selection, age upon inclusion (continuous), physical functioning (continuous), axillary surgery (SNP / ALND / No axillary surgery), hormonal therapy (yes / no), and bilateral breast surgery (yes/no) were removed from the model. The intercept of the final model was 1.07. All variables in the model were used for multiple imputation of missing variables, as well as level of education, pathological tumor stage and body image at 12 months.

*Significant odds ratios. [a] Both neoadjuvant as well as adjuvant chemotherapy. Some patients were also treated with targeted therapy. [b] Based on the EORTC QLQ-C30 questionnaire. [c] Based on the self-reported HADS-NL questionnaire, a score ≥8 indicates an increased risk of depressive disorders. [d] Including patients (n = 21) treated with partial breast irradiation. [e] Radiation therapy on periclavicular and / or axillary lymph nodes. Abbreviations: CI = confidence interval; OR = odds ratio; Ref. = reference category.

In the overall study population, the strong association between type of surgery and impaired body image disappeared in multivariable analysis. Therefore, in additional analysis, patients were stratified by use of chemotherapy to evaluate if the effect of type of surgery on body image differed between patients receiving chemotherapy in comparison to patients not receiving chemotherapy. Among patients not treated with chemotherapy, the association between body image and type of surgery remained in multivariable analysis: patients treated with mastectomy had a more than doubled risk of poor body image (OR 2.47, 95% CI 0.93-6.12) in comparison to those treated with breast conserving surgery. In the group of patients receiving chemotherapy, the association between surgery and body image disappeared in multivariable analysis (OR 0.94, 95% CI 0.51-1.69) (Supplementary table 3). A similar trend was seen for patients treated with breast reconstruction.

Discussion

This large prospective cohort study showed that the body image scores after breast cancer treatment were high. The number of patients that reported "very much" impact on any of the body image items was < 5% at every time point (i.e., baseline-48 months after radiotherapy). The proportion of patients that reported grade 3-4 impairment on one of the items increased slightly at 3 months after cohort inclusion, but improved again at 6 months and thereafter. Overall, the body image scores stabilized at one year after inclusion. Chemotherapy, lower baseline body image, lower baseline emotional functioning, and higher BMI were associated with poorer body image.

Several other studies evaluated body image after breast cancer treatment. In a prospective cohort study by Kindt et al, 175 patients were included (8). Similar to our study, all patients received radiotherapy with curative intent, 27% of the patients were treated with chemotherapy (39% in our study) and body image was assessed by means of the EORTC QLQ-BR23 prior to radiotherapy, during radiotherapy, immediately after radiotherapy and at 3 months, 1 year and 2 years after radiotherapy. Mean body image scores were high: 84.3 at baseline, 88.7 after 1 year follow up, and 85.9 at 2 years follow-up in comparison to respectively 85.8, 87.7, and 89.6 in our study. In the prospective study by Engel et al., patients (*n* = 1131) received yearly EORTC QLQ BR23 questionnaires during 5 year follow-up (7).

The mean body image score was 80.4 in the first year after diagnosis and improved to 82.8 in the second year after breast cancer diagnosis. As in our study, there was no significant change in body image score after the first year. Overall, body scores could potentially be slightly lower due to the outdated surgical techniques that were used in this study. The more recent cross-sectional study of Lagendijk et al. evaluated body image by means of the EORTC QLQ BR23 at median 5 years after surgery (19). The mean body image score was 75.9 (*n* = 496), which is lower than in our study. This study, however, may have possible selection bias, as patients were recruited through the website of the Dutch breast cancer association. For this reason, patients with poorer body image were potentially more likely to participate in this study. In our study, all breast cancer patients referred to our radiotherapy department were eligible for inclusion.

In addition, our study evaluated the association between poorer body image at 12 months after radiotherapy and different determinants. Chemotherapy was associated with poorer body image in our study. This may be caused by the long-term side effects of chemotherapy, such as cognitive impairment and fatigue (20–22). Our study also showed an association between a higher BMI and poorer body image. However unlike in our study, mastectomy is also often reported as important determinant for poorer body image (7,23). We did not observe an association between body image and type of surgery. This could partly be explained by an interaction between chemotherapy and type of surgery. In our study, the strength of the association between poorer body image and type of surgery depended on whether patients received chemotherapy. In the group of patients who did not receive chemotherapy, patients treated with mastectomy (with or without reconstruction) reported poorer body image in comparison to patients treated with lumpectomy. In the group of patients treated with chemotherapy, no association between type of surgery and impaired body image was seen. Potentially, the side effects of chemotherapy outweigh the effects of the surgery for patients receiving chemotherapy.

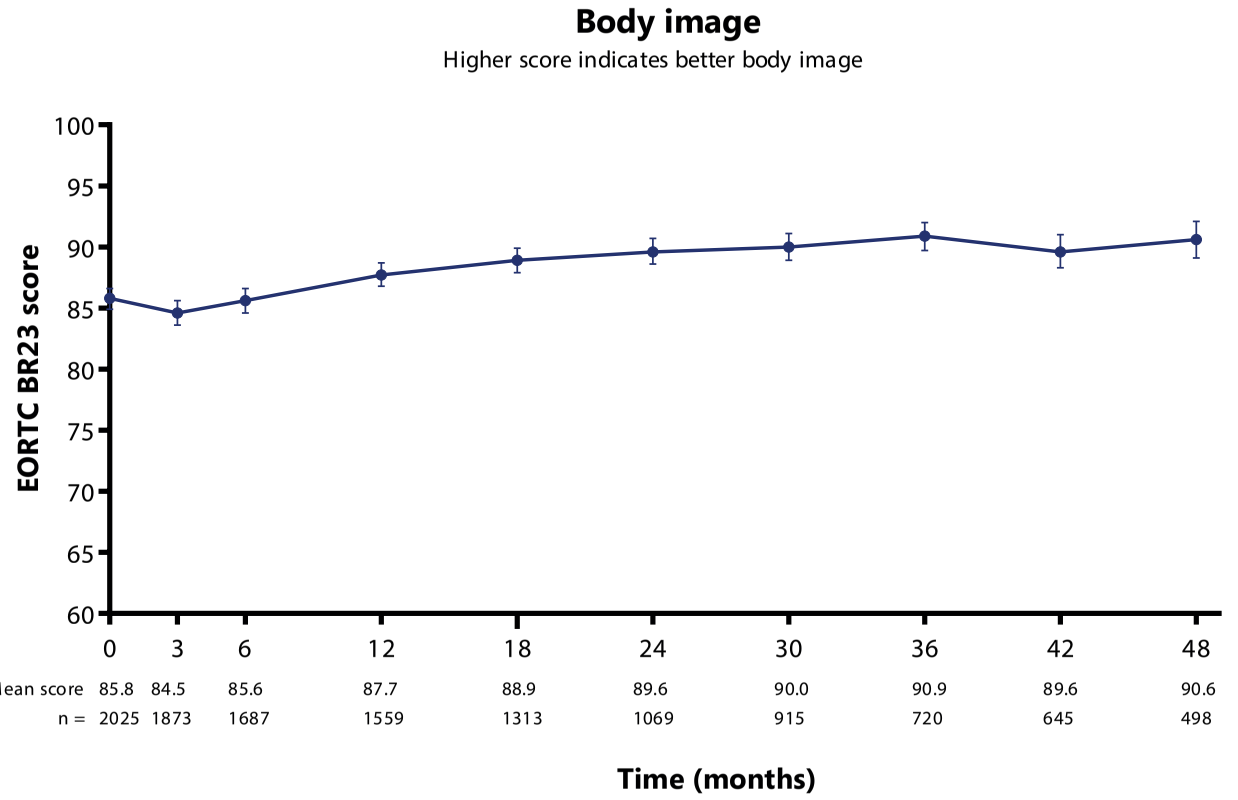
This study suffers from several limitations. First, as baseline body image was determined after surgery, it was not possible to determine the impact of breast cancer treatment on pre-treatment body image. Nevertheless, the proportion of patients that reported moderate to severe impairments in any body image domain was small. Second, no reference population was available for body image.

Consequently, it is unclear what the proportion of patients with poorer body image is in the general female population. Lastly, the non-response to the questionnaires was another limitation of this study. For example, the response to the 12 months questionnaire was 77%. In the study of Rooij et al, non-participants (n=3348) were matched to participants (*n* = 7368) included in the PROFILES registry – a Dutch non-commercial study registry (24). Using multiple imputation, EORTC quality of life scores of non-participants were predicted. On average, participants that completed the questionnaires scored higher quality of life scores on all functional domains. A possible implication could be that lower body image scores would have been reported by non-responders.

The results of this study are reassuring for women who are about to start their breast cancer treatment and who worry about its impact on attractiveness, femininity or dissatisfaction with physical appearance. Also, determinants associated with poorer body image in this manuscript (i.e., BMI, chemotherapy, baseline emotional functioning, and body image) could help clinicians to identify patients that may experience impaired body image after breast cancer treatment and to determine the necessity of (early) intervention.

In conclusion, with the current treatment options for breast cancer, the number of patients experiencing poor body image during and following breast cancer treatment is relatively low. The proportion of patients with impaired body image is the highest at 3 months after radiotherapy and stabilized at one year after radiotherapy. Lower baseline body image, lower emotional functioning, higher body mass index and chemotherapy were associated with poorer body image.

Supplementary figure 1. Body image scores in the UMBRELLA cohort during four years follow-up. Scores were based on the EORTC scoring manual. A higher score indicates a higher outcome.



Supplementary table 1. Baseline patient-, treatment and tumor characteristics of responders vs. non-responders to body image (evaluated by means of EORTC QLQ-BR23) at 12 months.

	Responders *n* = 1561	**Non-responders** *n* = 490
Age at inclusion (mean (SD))	58.1 (24-90)	57.7 (26-90)
Pathological tumor stage [a]		
0	81 (5)	33 (7)
In situ	181 (12)	44 (9)
1	907 (58)	287 (59)
2	308 (20)	96 (20)
3	38 (2)	16 (3)
4	3 (0.2)	0 (0)
Unknown	43 (3)	14 (3)
Type of surgery [a]		
Breast conserving surgery	1282 (82)	402 (82)
Mastectomy without breast reconstruction	153 (10)	52 (11)
Breast reconstruction	116 (7)	32 (7)
Unknown	10 (0.6)	4 (0.8)
Axillary surgery		
Axillary lymph node dissection	127 (8)	41 (8)
Sentinel Node Procedure	1258 (81)	412 (84)
No axillary treatment	127 (8)	30 (6)
Unknown	21 (1)	7 (1)
Bilateral breast surgery [b]	129 (8)	31 (6)
Systemic treatment [c]		
Chemotherapy	621 (40)	182 (37)
Hormonal therapy	747 (48)	227 (46)
Targeted therapy	172 (11)	48 (10)
No adjuvant treatment	621 (40)	205 (42)
Type of radiation therapy [a]		
Local without boost	614 (40)	194 (40)
Local with boost	490 (31)	126 (26)
Locoregional without boost [d]	204 (13)	66 (14)
Locoregional with boost [d]	129 (8)	54 (11)
Partial breast irradiation	16 (1)	5 (1)
Unknown	108 (7)	45 (9)
Body mass index (median (IQR)) [e]	25.5 (5.8)	25.5 (5.7)
Unknown	46 (3)	71 (15)
Baseline body image (mean (SD))	86.4 (19.0)	83.6 (22.1)
Unknown	13 (0.01)	13 (0.03)

Numbers are shown as *n* (%) unless stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and median (IQR) otherwise. Non-responders are defined as patients not responding to body image assessed by the EORTC-QLQ BR23 questionnaire at 12 months after inclusion.

[a] Total percentage other than 100% due to rounding. [b] Bilateral breast cancer or previous contralateral breast cancer. [c] Total percentage > 100% as patients may receive a combination of systemic treatment. [d] Including radiation therapy on periclavicular and/or axillary lymph nodes. [e] Weight / height^2.

Supplementary table 2. Crude and imputed patient-, tumor- and treatment characteristics.

	Crude dataset *n* = 2051	**Imputed dataset** *n* = 2051
Age at inclusion (mean (SD))	58 (24-90)	58 (24-90)
Type of surgery		
Breast conserving surgery	1684 (82)	1695 (83)
Mastectomy without breast reconstruction	205 (10)	207 (10)
Breast reconstruction	148 (7)	149 (7)
Unknown	14 (0.7)	
Axillary surgery [a]		
Axillary lymph node dissection	196 (10)	198 (10)
Sentinel Node Procedure	1670 (81)	1693 (83)
No axillary surgery	157 (8)	160 (8)
Unknown	28 (1)	
Chemotherapy		
Yes	803 (39)	803 (39)
No	1248 (61)	1248 (61)
Hormonal therapy [a]		
Yes	974 (47)	974 (48)
No	1077 (53)	1077 (53)
Type of radiation therapy [a,b]		
Local radiotherapy	1445 (71)	1528 (75)
Locoregional radiotherapy	453 (22)	523 (26)
Unknown	153 (8)	
Bilateral breast surgery [c]	160 (8)	160 (8)
Body mass index (median (IQR)) [d]	25.5 (5.7)	25.5 (5.9)
Unknown	117 (6)	
Highest level of education		
No schooling/secondary or vocational education	1072 (52)	1147 (56)
College, graduate or professional degree	871 (43)	904 (44)
Unknown	108 (5)	
Baseline body image (mean (SD))	85.8 (19.8)	85.8 (19.8)
Unknown	26 (0.1)	
Baseline emotional functioning (mean (SD))	76.8 (20.3)	76.7 (20.3)
Unknown	17 (0.01)	
Baseline physical functioning (mean (SD))	85.5 (15.9)	85.5 (15.9)
Unknown	6 (0.003)	
Depression scores, categorical [a,e]		
< 8	1775 (87)	1793 (87)
≥ 8	256 (13)	258 (13)
Unknown	20 (1)	

Numbers are shown as *n* (%) unless stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and median (IQR) otherwise.
[a] Total percentage other than 100% due to rounding. [b] Including radiation therapy on periclavicular and / or axillary lymph nodes. [c] Bilateral breast cancer or previous contralateral breast cancer. [d] Weight / height^2. [e] Based on the self-reported HADS questionnaire, a score ≥ 8 indicates an increased risk of depressive disorders.

Supplementary table 3. Subgroup multivariable regression analysis assessing the association between patient- and treatment characteristics and poorer body image after 12 months follow-up of breast cancer patients treated with chemotherapy and not treated with chemotherapy.

	Chemotherapy OR (95% CI)	*n* = 803	**No chemotherapy** OR (95% CI)	*n* = 1248
Type of surgery				
Breast conserving surgery	Ref.	541	Ref.	1153
Mastectomy without breast reconstruction	0.94 (0.51-1.69)	149	2.47 (0.93-6.12)	59
Breast reconstruction	1.40 (0.77-2.50)	113	2.62 (0.86-7.20)	36
Body mass index	1.05 (1.01-1.10)*	803	1.07 (1.02-1.12)*	1248
Baseline body image [a]	0.97 (0.96-0.98)*	803	0.96 (0.95-0.97)*	1248
Baseline emotional functioning [a]	0.98 (0.97-0.99)*	803	0.98 (0.97-1.00)*	1248
Depression scores, categorical [b]				
≤8	Ref.	693	Ref.	1098
>8	1.23 (0.64-2.33)	110	1.79 (0.91-3.44)	150
Type of radiotherapy				
Local radiotherapy	Ref.	671	Ref.	881
Locoregional radiotherapy [c]	1.35 (0.86-2.13)	132	0.63 (0.27-1.39)	367

Shown results are from multivariable logistic regression analysis after multiple imputation.
*Significant odds ratios. [a] Based on the EORTC QLQ-C30 questionnaire. [b] Based on the self-reported HADS questionnaire, a score ≥ 8 indicates an increased risk of depressive disorders.
[c] Including radiation therapy on periclavicular and / or axillary lymph nodes.
Abbreviations: CI = confidence interval; OR = odds ratio; Ref. = reference category.

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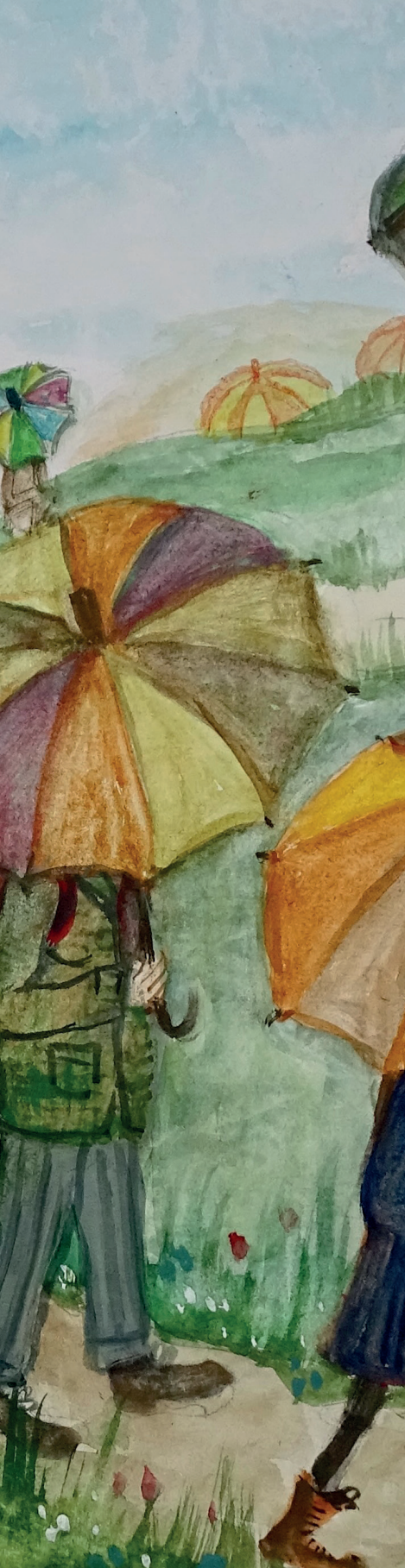

4

Factors associated with late local radiation toxicity after postoperative breast irradiation – a systematic review

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Submitted

Abstract

Purpose: To assess determinants associated with late local radiation toxicity in patients treated for breast cancer.

Methods: A systematic review was performed. All studies reporting ≥ 2 variables associated with late local radiation toxicity after treatment with postoperative whole breast irradiation were included. Systematic reviews, cohort studies and cross-sectional studies were eligible designs. Study characteristics and definitions of determinants and outcome measures were extracted. If possible, the measure of association was extracted.

Results: Twenty-one studies were included in this review. Six out of seven studies that focused on the association between radiotherapy (boost) dose or irradiated breast volume and late radiation toxicity found significant results. Tumor bed boost was associated with late radiation toxicity, fibrosis and / or edema in 6/12 studies. Lower age was associated with late breast toxicity in one study, whilst in another study, higher age was significantly associated with breast fibrosis. Also, no association between age and late radiation toxicity was found in 8/12 studies. Similar inconsistent results were found in the association between late radiation toxicity and other patient-related factors (i.e., breast size, diabetes mellitus) and surgical and systemic treatment related factors (i.e., complications after surgery, chemotherapy, time between surgery and radiotherapy).

Conclusion: In modern 3D radiotherapy, radiotherapy (boost) dose and volume are – like in 2D radiotherapy – associated with late local radiation toxicity, such as breast fibrosis and edema. Treatment de-escalation, e.g., partial breast irradiation in selected patients might be important to decrease late local toxicity without compromising locoregional control and survival.

Introduction

Due to early detection and improved treatments, 5-year overall survival of women diagnosed with breast cancer in the Netherlands approaches 90% (1). The large and growing number of breast cancer survivors calls for improved understanding of late effects of breast cancer treatment (2,3). For example, patients treated with radiotherapy might develop late radiation toxicity (4). Late local radiation toxicity is characterized by breast or chest wall pain, breast fibrosis, impaired arm movement, breast or arm edema or disappointing cosmetic results from at least 3 months after radiotherapy (4).

From studies investigating 2D radiotherapy, we know that higher radiotherapy dose and tumor bed boost are associated with more late radiation toxicity (5,6). In the 3D era of radiation therapy, various studies investigated the incidence of late toxicity within these new techniques to assess safety and long-term side-effects. Simultaneously, new radiotherapy techniques and treatment de-escalation have been developed, such as implementation of intensity modulated radiotherapy-techniques, concurrent instead of sequential boost techniques and hypofractionation (7–11).

In order to evaluate the toxicity profiles of these radiotherapy innovations, it is important to take prognostic factors that influence late toxicity into account. Currently, no overview of clinical or radiotherapy related factors associated with late radiation toxicity in the current 3D radiotherapy is known. Therefore, a systematic literature review was performed. The aim of this systematic review was to assess which factors were associated with late radiation toxicity of the breast in breast cancer patients.

Methods

Search strategy

A systematic literature search was performed in Pubmed and Embase on 21-12-2020. The following search terms, medical subject headings terms (MeSH) and their respective synonyms were combined: breast cancer AND late toxicity AND radiotherapy. Search terms were restricted to title and abstract. A complete search string is attached in Supplementary material A. The preferred reporting

items for systematic reviews and meta-analysis (PRISMA) guidelines were followed (12). Both title and abstracts screening on eligibility criteria and full-text evaluation was performed independently by two authors. Disagreement on eligibility was solved by discussion and consensus.

Eligibility criteria

Studies conducting research on predictive variables associated with late local radiation toxicity in irradiated breast cancer patients were eligible for inclusion. Predictive factors associated with late radiation toxicity of the skin might be correlated (e.g., chemotherapy and hormonal therapy). Therefore, only studies comparing multiple (i.e., ≥ 2) potential predictive variables were included. As late radiation toxicity is characterized by various symptoms, potentially the definition of late radiation toxicity differs per study. Subsequently, also studies evaluating the association between predictive variables and breast fibrosis, breast- or chest-wall pain, impaired arm movement or breast / arm edema after radiotherapy were included. All systematic reviews, cohort studies, including cohort studies in a trial population, and cross-sectional studies were eligible designs. Case reports were excluded, as well as studies performed prior to 2005, since 3D radiotherapy treatment performed nowadays is associated with different toxicity profiles than 2D radiotherapy performed prior to 2005. Consequently, studies reporting 2D, but published after 2005 radiotherapy were also excluded.

Since external beam radiotherapy volumes and dosimetry in organs at risk differ from those in brachytherapy, cobalt radiotherapy, intra-operative radiotherapy and proton radiotherapy, studies using these radiotherapy techniques were excluded. As irradiated breast volume is different in partial breast irradiation, resulting in less skin toxicity, studies conducting research on breast cancer patients treated with partial breast irradiation were excluded (13,14). This review focuses on local toxicity after post-operative irradiation in breast cancer patients. Consequently, studies investigating cardiotoxicity, lung toxicity and plexopathy caused by radiotherapy were excluded. The aim of this review was to assess the association between patient- or treatment-related factors and late radiation toxicity. Therefore, studies conducting research on the association between genetic factors and late radiation toxicity were excluded. In addition, studies with a follow-up < 12 months after treatment were excluded. Studies written in other languages than Dutch and English were excluded.

Critical appraisal

The risk of bias of the included studies was assessed using the QUIPS risk of bias tool for prognostic studies (15). In accordance with the Quality In Prognostic Studies (QUIPS) tool, risk of bias for all included studies was evaluated on six domains: "study participation", "study attrition", "prognostic factor measurement", "outcome measurement", "study confounding" and "statistical analysis and reporting". Each domain was rated "low", "medium" or "high" in accordance with proposed guidelines of Hayden et al. (15).

Data extraction and data analysis

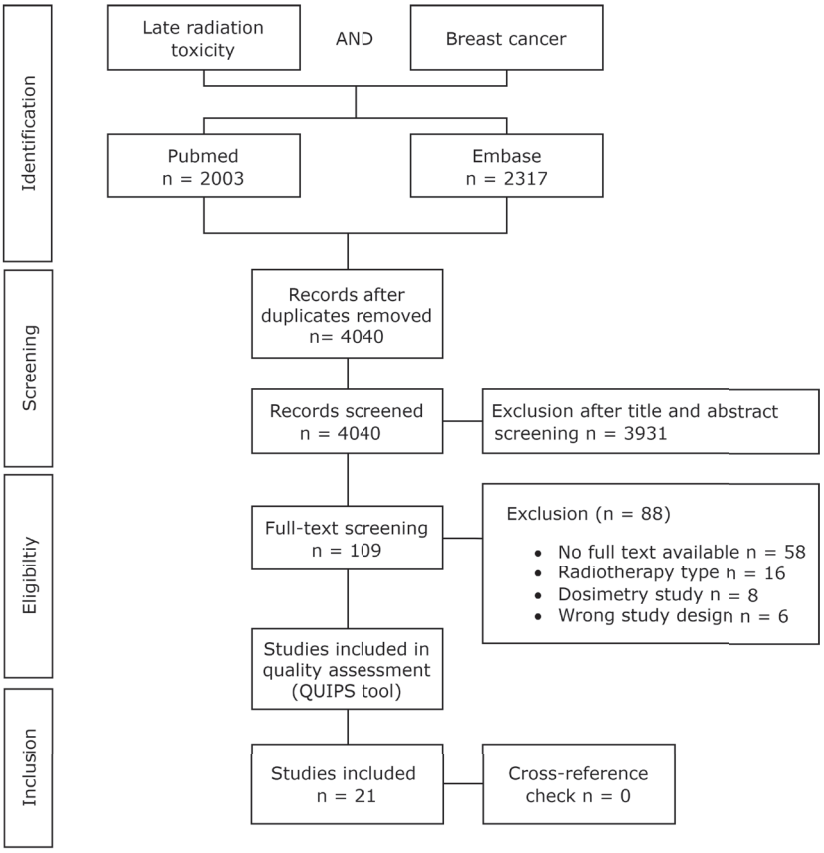
Characteristics extracted from the included studies were publication year, number of included patients, median age of participants, gender, tool used to determine toxicity, median follow-up duration and study design. Also, radiotherapy planning technique, dose fractionation scheme and total radiotherapy dose were extracted from all studies. The definition of all reported risk factors for each study was extracted. If possible, the measurement of association and strength of association for each variable was extracted. In case both univariable and multivariable analysis were performed, the results of the multivariable model were extracted as multivariable analysis was considered more reliable. When no measure of association was reported (e.g., only a *p*-value was provided), the strength of association was shown as not reported.

Results

The search strategy resulted in 4040 records. After exclusion of irrelevant records and records not meeting the in- and exclusion criteria, 21 studies were included in this review (Figure 1) (16–36).

In accordance with the QUIPS tool, a high risk of bias was assigned to most studies due to high risk of bias in at least one of the subdomains of the QUIPS tool (Figure 2). High risk of bias was mostly caused by lack of description of missing data or lack of attempts to collect data from missing cases. Risk of bias assessment did not lead to exclusion of the studies for this review.

Figure 1. Flowchart of selected studies to evaluate which determinants were associated with late radiation toxicity in breast cancer patients.



The included studies were published between 2007 and 2020. The majority (*n* = 17) of the studies had a median follow-up of > 24 months (Table 1). In total, 8572 patients were included in all studies (range 67-1014 patients per study) and median age ranged from 49-74 years. In most studies, toxicity was assessed by a physician with Common Terminology Criteria for Adverse Events (CTCAE) (37) (*n* = 6), Radiation Therapy Oncology Group (RTOG) criteria (38) (*n* = 12) or Late Effects Normal Tissue-Subjective Objective Management Analytic (LENT-SOMA) (39) (*n* = 3). Most studies had a prospective design (*n* = 13/21, 62%). All patients were treated with post-operative whole breast irradiation (Table 2). In all studies patients were treated with 3D conformal radiotherapy, forward planned IMRT (*n* = 16) or inverse planned IMRT/VMAT (*n* = 5). Factors associated with late radiation toxicity were categorized into patient characteristics, factors related to radiotherapy, factors related to surgical or systemic treatment or other (Table 3).

Figure 2. Risk of bias assessment for included studies using the QUality In Prognostic Studies (QUIPS) tool.

Author	Overall	Participation	Attrition	Prognostic factor	Outcome	Confounding	Analysis and reporting
Barnett	▣	□	▣	▣	□	□	□
Bergom	■	▣	■	▣	□	□	▣
Bronsart	■	■	■	▣	□	▣	▣
Ciamella	■	□	■	▣	□	□	□
De Rose	■	□	■	▣	□	▣	■
De Rose (2020)	▣	□	▣	□	□	□	□
De Santis	▣	□	▣	▣	□	□	□
Digesu	■	▣	■	▣	□	□	□
Hannan	■	▣	■	▣	■	▣	■
Hille-Betz	■	▣	■	■	□	□	■
Hosni	■	□	■	■	▣	▣	▣
Ishiyama	■	■	■	▣	▣	□	▣
Joseph	▣	▣	□	□	▣	□	□
Kelemen	■	□	■	▣	▣	□	□
Keller	■	□	■	▣	□	□	□
Lazzari	■	□	■	▣	□	□	□
Lilla	□	□	□	□	□	□	□
Meattini	■	□	■	▣	□	□	□
Palumbo	■	□	□	■	□	□	■
La Rocca	■	□	■	▣	□	□	▣
Yu	■	□	■	■	□	▣	▣

■ High risk of bias ▣ Medium risk of bias □ Low risk of bias

Table 1. Study characteristics.

Study (year)	Patients (*n*)	FU duration (months)[a]	Age (years)[a]	Toxicity assessment	Study design	
Barnett (2011)	1014	24 (for all patients)	NR	RTOG criteria	RCT	Prospective
Bergom (2012)	109	40.3 (mean 45.9, range 1-127)	61 (27-91)	CTCAE 3.0	Cohort	Prospective
Bronsart (2017)	832	76.8 (18-148.8)	61.5 (29-90)	CTCAE 3.0	Cohort	Prospective
Ciamella (2014)	212	34 (8-44)	63 (39-88)[b]	RTOG criteria	Cohort	Prospective
De Rose (2016)	144	37 (24-55)	62 (30-88)	CTCAE 4.0	Cohort	Prospective
De Rose (2020)	831	2 years (at least)	60 (27-88)	RTOG and CTCAE	Cohort	Unclear
De Santis (2016)	537	32	74 (46-91)	RTOG criteria	Cohort	Prospective
Digesu (2018)	447	52 (3-115)	63 (IQR 56-71)	RTOG criteria	Cohort	Retrospective
Hannan (2012)	129	9.87 (mean)	NP	RTOG criteria	Cohort	Retrospective
Hille-Betz (2016)	159	19.4 (11.3-44.8)	58 (36-86)	LENT-SOMA	Cohort	Retrospective
Hosni (2017)	67	25 (11-34)	49 (31-69)	RTOG criteria	Cohort	Prospective
Ishiyama (2006)	193	45.6 (8-132)	50 (27-77)[b]	LENT-SOMA	Cross-sectional	Prospective
Joseph (2020)	175	73.1 (4.2-101.8)	58 (41-77); 59 (41-82)[c]	RTOG criteria	RCT	Prospective
Kelemen (2012)	198	28.8 (14.4-70.8)	62 (25-89)[b]	4-point Likert	Cohort	Retrospective
Keller (2012)	946	31 (1-97)	58 (31-91)	Unclear	Cohort	Prospective
Lazzari (2017)	215	72	68 (60-75)[b]	RTOG criteria	Cohort	Retrospective
Lilla (2007)	421	51 (36-77)	61-70 (31-91)[d]	RTOG criteria and LENT-SOMA	Cohort	Prospective
Meattini (2019)	786	45.6 (24-102)	50 (22-60)	RTOG criteria	Cohort	Retrospective
Palumbo (2019)	220	12	62 (34-88)	CTCAE 4.03	Cohort	Prospective
La Rocca (2019)	794	48.3 (6-114)	74 (65-91)	RTOG criteria	Cohort	Prospective
Yu (2017)	143	21.4 (3.8-61.6)	65 (44-91)	CTCAE 4.3	Cohort	Retrospective

[a] Numbers are shown as median (range), unless stated otherwise. [b] Mean age [c] In respectively inversed planned and helical tomography groups [d] Absolute number not provided, median extracted from data provided.
Abbreviations: 3DCRT 3D conformal radiotherapy; CTCAE common terminology criteria for adverse events; IMRT intensity modulated radiotherapy; ILD isocentric lateral decubitus position; IQR inter-quartile range; LENT-SOMA late effects in normal tissues – subjective, objective, management and analytic score; RCT randomized controlled trial; RTOG radiation therapy oncology group; RTP radiotherapy; SIB simultaneous integrated boost; VMAT volumetric modulated arc radiotherapy; WBI whole breast irradiation.

Table 2. Overview of type of radiotherapy techniques and dose fractionation schedule in the included studies.

Study (year)	RTP technique	Prescribed RT dose	Boost	Nodal irradiation
Barnett (2011)	3DCRT	40 Gy in 15 fractions	Some patients	Some patients
Bergom (2012)	3DCRT prone position	45-50 Gy, fractionation unclear.	72% of patients (average 10Gy in 5 fractions)	Unclear
Bronsart (2017)[a]	3DCRT (in lateral isocentric decubitus position)	47% 50Gy + boost 18% 50 Gy in 25 fractions 26% 40-42.6 Gy in 13-15 fractions 10% 30 Gy in 5 fractions	47% 16 Gy sequential boost in 33 fractions	Unclear
Ciamella (2014)	3DCRT	40.05 Gy in 15 fractions	26% of patients received sequential boost of 9 Gy in 3 fractions.	Unclear
De Rose (2016)	VMAT	40.5 Gy	48.0 Gy concomitant boost in 15 fractions.	None
De Rose (2020)	VMAT	40.5 Gy	48 Gy sequential integrated boost, 2.7 of 3.2 Gy/fraction	Unclear
De Santis (2016)	3DCRT	42.4 Gy in 16 fractions	73% of patients receiving additional sequential boost (10 Gy in 4 fractions boost or 16 Gy in 8 fractions).	None
Digesu (2018)[b]	3DCRT vs. forward planning IMRT	50.4Gy in 28 fractions 40 Gy in 16 fractions	sequential boost 10 Gy in 4 fractions concomitant boost 4 Gy	None
Hannan (2012)	Inverse planning IMRT	42.4 Gy in 16 fractions	9.6 Gy sequential boost in 4 fractions	None
Hille-Betz (2016)[a]	3DCRT	57% 50 Gy in 25 fractions 43% 50.4 Gy in 28 fractions	32% of the patients received sequential boost	Unclear
Hosni (2017)	3DCRT	40Gy in 15 fractions	concomitant 3 Gy boost in 3 fractions	Unclear
Ishiyama (2006)	3DCRT	50 Gy in 25 fractions	Depending on protocol 10-16 Gy boost	Unclear
Joseph (2020)	Helical Tomography IMRT vs. inverse planning IMRT	50 Gy in 25 fractions	None	None
Kelemen (2012)	3DCRT	50 Gy in 25 fractions	Some patients	Some patients
Keller (2012)[b]	Inverse planning IMRT	Median 46 Gy, fractionation unknown	99% of patients received concomitant boost (dose unknown)	Some patients

Lazzari (2017)	3DCRT	42.56 Gy in 16 fractions	None	Unclear
Lilla (2007)[b]	3DCRT	50 Gy in 25 fractions 50.4 Gy in 28 fractions 56Gy with 2 Gy per fraction	5-20 Gy sequential boost	Unclear
Meattini (2019)[a]	3DCRT	43% 40 Gy in 15 fractions	Sequential 9-18.69 Gy boost in 3-7 fractions (some patients)	Unclear
		57% 50 Gy in 25 fractions	Sequential 10-20 Gy boost in 5-10 fractions (some patients)	
Palumbo (2019)	3DCRT	42.4 Gy in 16 fractions	Sequential boost 10.6-13.25 Gy in 4-5 fractions (some patients)	
La Rocca (2019)	3DCRT	42.4 Gy in 16 fractions	25% received sequential boost with 10-16 Gy in 4-8 fractions	Unclear
Yu (2017)	3DCRT	42.5 Gy in 16 fractions	8 Gy in 3 fractions	Unclear

Whole breast irradiation in all studies. If not reported in the table, dose or fractionation was unknown.
[a] Not all patients received same radiotherapy dose. Proportion of patients receiving certain dose shown in third column.
[b] Different radiotherapy doses administered, proportion of patients receiving certain dose unclear.
Abbreviations: 3DCRT 3D conformal radiotherapy; IMRT intensity modulated radiotherapy; RT radiotherapy; SIB simultaneous integrated boost; VMAT volume modulated arc therapy; WBI whole breast irradiation.

Table 3. Overview of different domains of late radiation toxicity in relation to the summarized risk factors

		Radiotherapy			**Surgery and systemic treatment**						**Patient characteristics**					**Other** [a]
	Study	Increased dose or irradiated volume	RT boost (dose)	Acute toxicity	RT-surgery interval	Surgical complications	ALND	Endocrine therapy	Chemotx	Other LRT symptoms	Age	Breast volume	Tumor location	BMI	Diabetes mellitus	
GRT	Ciamella	S/NSb	S/NSb	-	-	NS	-	-	S/NSb	-	NS	NS	-	-	NS	NS
	de Rose	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	de Rose (2020)	NS	S	-	-	-	-	NS	NS	-	NS	S	-	-	-	S
	Digesu	S	-	-	-	-	-	NS	NS	-	-	-	-	-	NS/Sc	S
	Hannan	S	-	-	-	-	-	-	-	-	-	S	-	S	-	S
	Hosni	-	-	-	-	-	-	-	-	-	S	NS	-	-	S	-
	Keller	S	S	-	-	-	-	S	S	-	-	-	-	-	-	-
	Lazzari	S	-	-	-	-	-	-	NS	-	-	NS	-	-	-	S
	Palumbo	-	NS	-	-	-	NS	NS	NS	-	-	-	-	-	NS	NS
	Yu	-	NS	-	-	S	-	-	-	-	NS	-	-	NS	-	S/NS
Pain	Barnett	-	S	S	-	S	-	-	-	-	S	-	-	-	-	-
	de Rose (2020)	-	NS	-	-	-	-	-	-	-	-	NS	-	-	-	NS
	Hille-Betz	NS	-	-	-	-	-	-	-	S	-	-	-	-	-	-
	Ishiyama	-	S	-	NS	-	-	-	NS	-	NS	-	NS	-	-	NS
Breast fibrosis	Bergom	-	NS	-	-	-	NS	-	NS	-	-	NS	-	NS	-	NS
	Bronsart	S/NS	-	-	-	-	-	-	NS	-	NS	NS	-	-	-	-
	de Santis	NS	NS	-	-	-	-	-	NS	-	-	NS	-	-	NS	-
	Hille-Betz	NS	-	-	S	-	-	-	NS	-	-	S	-	-	-	-
	Ishiyama	-	NS	-	S	-	-	-	NS	-	NS	-	NS	-	-	NS
	Joseph	-	-	-	-	-	-	NS	NS	NS	NS	S	-	-	-	NS
	Kelemen	S	-	-	-	-	S	-	-	S	-	-	-	-	-	S
	Lilla	-	-	-	-	-	-	-	-	-	S	-	-	-	-	S
	Meattini	NS	S	-	-	-	-	-	-	-	-	S	-	-	-	S/NS
	La Rocca	-	S	-	-	-	-	-	NS	-	NS	-	-	-	-	-

Breast or arm edema	Barnett	-	S	S	-	-	-	-	-	-	S	S	-	-	-	-
	Hille-Betz	NS	-	-	NS	-	S	-	-	-	-	S	-	NS	-	NS
	Ishiyama	-	NS	-	NS	-	-	-	S	-	NS	-	S	-	-	NS
	Kelemen	S	-	-	-	-	S	-	-	-	-	-	-	-	-	-
	Keller	S	S	-	-	-	-	S	S	-	-	-	-	-	-	-
	Meattini	S	S/NSc	-	-	-	-	-	-	-	-	NS	-	-	-	NS
	La Rocca	-	S	-	-	-	-	-	-	-	NS	-	-	-	-	NS

[a] Depending on boost/no boost group. [b] Depending on respectively subacute or skin toxicity. [c] Depending on administered dose;
Abbreviations: BMI body mass index; Chemotx chemotherapy; GRT late radiation toxicity; LRT late radiation toxicity; NS no significant association, RT radiotherapy; S significant association; - Association not studied

Association between radiotherapy and late local radiation toxicity

Seven studies evaluated the association between increased radiotherapy volume or dose and late radiation toxicity (23,25–27,30,32,36) (Table 3). Six out of these seven studies found a significant association and the association measurement was quantified in 4 studies (Table 4). An association was seen between general radiation toxicity and breast volumes receiving >107% of the prescribed radiotherapy dose (OR 6.27 95% CI 1.34-29.37) (30). Also, breast volumes receiving >110% of prescribed dose was correlated with higher late toxicity rates (R 0.402) (23). In addition, they found that a planned target volume (PTV) > 1300 cc was highly correlated with general radiation toxicity in another study (R 0.955). In addition, an association between increased PTV volume and grade 2 fibrosis was shown (HR 1.14 95% CI 1.01-1.28) (32). Another study defined radiation toxicity as either edema, erythema or telangiectasia. They found a significant association between late radiation toxicity and an increase in clinical target volume (CTV) (respectively < 500 vs. 500-900 vs. > 900 OR 1.9 (95% CI not reported) and 3.0 (95% CI 2.0-4.5)) (36).

Several studies found a significant association between higher radiotherapy dose and breast fibrosis (Table 5). A radiotherapy dose of 50 Gy in 25 fractions resulted in a 12.5 times higher odds ratio than a dose of 30 Gy in 5 fractions (95% CI 2.73-57.13) (16). However, 3 other studies found no significant association between radiotherapy dose or irradiated volume and fibrosis (Supplementary material C) (19,31,33). Two studies found a significant association between (breast) pain and administration of additional radiotherapy boost on the tumor bed (respectively OR 1.38 (95%CI 1.04-1.83) and 3.30 (95% CI 1.26-8.66)) (Table 4) (17,34). In addition, the administration of an additional radiotherapy boost on the tumor bed was significantly associated with higher breast fibrosis scores (OR 1.70 95% CI 1.16-2.48) (Table 5) (21). Also, one study found that an increase in boost volume was associated with more fibrosis (OR 1.07 95% CI 1.00-1.14) (35). Nevertheless, this association was not seen in three other studies (Supplementary material C) (28,31,34).

Table 4. Significant association between various risk factors and late radiation breast toxicity ≥12 months after whole breast irradiation.

Author (year)	Associated risk factors	Measure of association	Estimation of association
Ciamella (2014)	Skin toxicity	OR	
	Boost		3.06 (1.28-7.30)
	Subcutaneous toxicity		
	Chemotherapy		2.59 (1.17-5.72)
	Breast volumes receiving > 104% vs. < 100%		0.08 (0.1-0.52)
	Breast volumes receiving > 107% vs. < 100%		6.27 (1.34-29.37)
de Rose (2016)	PTV	NR	
de Rose (2020)	Boost volume > 70cm^3	OR	2.14 (1.26-3.62)
	Treated skin area[a] > 400 cm^2		2.16 (1.12-4.19)
	Breast size > 1500cm^3		2.10 (1.03-4.30)
Digesu (2018)	Skin	OR	
	Tobacco smoking		2.15 (1.38-3.34)[b]
	PTV volume		1.12 (1.07-1.18)[b]
			1.27 (1.15-1.41)[c]
	Subcutaneous		
	3DCRT vs. Mara-1[d] technique		2.18 (1.50-3.18)[b]
			3.01 (1.08-8.42)[c]
	Diabetes		1.65 (1.01-2.71)[b]
	PTV volume		1.14 (1.08-1.20)[b]
			1.14 (1.01-1.28)[c]
Hannan (2012)	Prone vs. supine position	R	NR
	Large breast vs small breast		NR
	BMI		0.38
	PTV		0.027
Hosni (2017)	Age > 50y vs. < 50y	OR	NR (1.01-1.20)
	DM[d]		NR (0.00-0.20)
Keller (2012)	RT Boost dose (> 16 vs. < 16 Gy)	OR	2.4 (1.5-3.7)
	RT vs. RT combined with chemotherapy and endocrine therapy		1.9 (1.2-2.9)
	CTV 500-900 vs. <500		1.9 (NR)
	CTV ≥900 vs. <500		3.0 (2.0-4.5)
	Boost energy ≥ 12MeV vs. ≤ 10		1.8 (1.3-2.7)
Lazzari (2017)	PTV < 1300 vs. > 1300 cc	R	0.955
	Breast volumes receiving > 110%[f]		0.402
	Surgery good vs. poor result		0.455
Palumbo (2018)	None	HR	NA
Yu (2017)[g]	Re-excision	NR	
	Postoperative complication		

All shown variables were significantly associated with late radiation toxicity. See supplementary material for non-significant variables.
[a] Skin surface surrounding irradiated area receiving at least 20Gy [b] Estimation for Grade 1 toxicity. [c] Estimation for grade 2 toxicity. [d] Modulated Accelerated hypofractionated Radiotherapy. [e] No vs. yes [f] < 10% vs. > 10% [g] Results of univariable analysis, no multivariable analysis performed. Abbreviations: 3DCRT 3D conformal radiotherapy; BMI body mass index; CTV clinical target volume; DM diabetes mellitus; MeV mega electrovolt; NA not applicable; NR not reported; OR odds ratio; PTV planned target volume; R pearsons correlation; RT radiotherapy.

Table 5. Significant association between different risk factors and breast fibrosis in irradiated breast cancer patients ≥12 months after whole breast irradiation.

Author (year)	Associated risk factors	Measure of association	Strength of association
Bergom (2012)	None	NA	
Bronsart (2017)	Radiotherapy dose 50 Gy vs. 30 Gy	OR	12.5 (2.73-57.13)
de Santis (2016)	None	NA	
Hille-Betz (2016)	Ptosis grade 2/3 or C-cup size	NR	0.02[a]
	Interval to radiotherapy		0.03[a]
Ishiyama (2006)[b]	Time after surgery (< 2 vs. > 5 years)	OR	0.06 (0.005-0.83)
Kelemen (2012)	100cm^3 increase irradiated breast volume	OR	1.07 (1.00-1.14)
	10cm^3 increase boost volume		1.12 (1.09-1.33)
	Photon boost	NR	
	Edema	NR	
	PTV	NR	
Joseph (2020)	Breast volume (<1032cm^3 vs. >1032 cm^3)	OR	1.01 (1.00-1.03)
Lilla (2007)	Age		1.06 (1.01-1.11)
	Allergy		2.45 (1.11-5.51)
Meattini (2019)	Extensive intraductal component	OR	2.15 (1.17-3.98)
	Tumor grade 2 vs. 1		0.54 (0.29-0.99)
	Tumor grade 3 vs. 1		0.29 (0.11-0.74)
	Breast size > 492 cc		2.64 (1.50-4.65)
	Boost dose > 10 Gy		6.76 (2.04–22.45)
La Rocca (2019)	Boost	OR	1.70 (1.16-2.48)

All shown variables were significantly associated with late radiation toxicity. See Supplementary material for non-significant variables.
[a] *p*-value [b] Reported outcome is breast firmness. Abbreviations: NA not applicable; NR not reported; OR odds ratio; PTV planned target volume;

Administration of a sequential boost to the tumor bed was associated with higher edema scores in the studies by Barnett et al., La Rocca et al. and Meattini et al. (respectively OR 1.71 95% CI 1.20-2.43, 1.70 95% CI 1.08-2.67 and 9.02 (95% CI 1.21–67.45)) (Table 7) (17,19,21). In addition, a significant association between higher boost volume and edema was seen in one study (OR 1.21 95%CI 1.09-1.33) (35). One study showed significantly more edema when the boost dose was > 16 Gy vs. < 16 Gy (OR 1.9 95% CI 1.2-3.0) (36). There were two studies that found no significant association between boost administration or boost dose and edema (19,34).

Table 6. Significant association between different risk factors and breast pain in irradiated breast cancer patients ≥ 12 months after breast cancer treatment.

Author (year)	Associated risk factors	Measure of association	Estimation of association
Barnett (2011)	Breast pain	OR	
	Boost		1.38 (1.04-1.83)
	Age		0.81 (0.70-0.94)
	Oversensitivity		
	Postoperative infection		1.78 (1.27-2.49)
	Acute toxicity		1.29 (1.02-1.64)
De Rose (2020)	None	NA	
Hille-Betz (2016)	Lymphedema arm[b]	OR	3.9 (1.17-13.5)
Ishiyama (2006)	Boost	OR	3.30 (1.26-8.66)

All shown variables were significantly associated with late radiation toxicity. See supplementary material for non-significant variables.
[a] Shoulder / arm pain. Abbreviation: OR odds ratio

Table 7. Significant association between different risk factors and edema in irradiated breast cancer patients ≥12 months after breast cancer treatment.

Author (year)	Associated risk factors	Measure of association	Strength of association
Barnett (2011)	Breast volume (1L increase)	OR	3.65 (2.54-5.24)
	Age		1.44 (1.18-1.76)
	Boost		1.71 (1.20-2.43)
	Acute toxicity[a]		1.51 (1.13-2.02)
Hille-Betz (2016)	Arm edema	OR	
	Axillary lymph node dissection		4.3 (1.4-13.58)
	Breast edema		
	Axillary lymph node dissection		10.59 (2.1-53.36)
	Ptosis grade 2/3 or bra size>C		5.34 (1.2-24.12)
Ishiyama (2006)[b]	Chemotherapy	OR	5.64 (1.18-26.98)
	Supraclavicular RT[c]		16.03 (3.06-84.01)
	Parasternal RT[c]		13.92 (2.16-89.90)
Kelemen (2012)	10cm3 increase boost volume	OR	1.21 (1.09-1.33)
	Tumor size	NR	
	Axillary lymph node dissection	NR	
	Fibrosis	NR	
	Asymmetry	NR	
Keller (2012)	Boost dose (>16 vs.<16gy)	OR	1.9 (1.2-3.0)
	Boost energy >12MeV vs. <10MeV		1.8 (1.3-2.7)
	RTP alone vs. RTP, chemotherapy and endocrine therapy		2.3 (1.4-4.0)
	RTP alone vs. RTP and endocrine therapy		1.8 (1.1-2.9)
	CTV <500 vs. 500-900cc		2.1 (1.4-3.2)
	CTV <500 vs. >900 cc		4.7 (2.9-7.5)
Meattini (2019)	Hypofractination	OR	0.18 (0.04-0.75)
	Boost dose >10Gy		15.43 (2.08–114.3)
La Rocca (2019)	Boost	OR	1.70 (1.08-2.67)

All shown variables were significantly associated with late radiation toxicity. See supplementary material for non-significant variables. [a] Per unit increase in RTOG score measured at week 3; [b] Reported outcome is thickening of arm; [c] No vs. yes. Abbreviations: CTV clinical target volume; L liters; NR not reported; OR odds ratio; RT radiotherapy

Association between surgical treatment or systemic treatment and late radiation toxicity

Two studies found an association between the occurrence of surgical complications and late radiation toxicity (Table 3) (17,24). Barnett et al. found a significant association between postoperative infection and late oversensitivity of the breast after radiotherapy and (OR 1.78 95% CI 1.27-2.49) (Table 6) (17). Huang et al. found a significant association between postoperative complications and general radiation toxicity (Table 4) (24). However, Ciammella et al found no association between surgical complications and late radiation toxicity (Supplementary table B) (30).

An association between axillary lymph node dissection and both arm and breast edema was seen in two studies (9,12). Chemotherapy was associated with increased edema scores in one study (OR 5.64 95% CI 1.18-26.98) (34). Also, one study reported an increased OR for administration of chemotherapy and endocrine therapy of 2.3 (95% CI 1.4-4.0) in comparison to radiotherapy only (Table 7) (36). However, 9/12 studies showed no significant association between chemotherapy and radiation toxicity. One study found a significant association between chemotherapy and edema, however no significant association between chemotherapy and pain or fibrosis (Table 7, Supplementary material C) (34). Endocrine therapy without chemotherapy increased the risk of edema with 1.8 (95% CI 1.1-2.9) (Table 7) (36).

Patient characteristics associated with late radiation toxicity

In one study, lower age was associated with general radiation toxicity and breast pain (Table 4) (19). In another study higher age was significantly associated with breast fibrosis (Table 5) (18). The other 7/10 studies investigating the association between late radiation toxicity and age found no significant association (Table 3) (16,21,24,27,29,30,34).

Larger breast size was associated with an increased risk of late radiation toxicity. A strong association between breast size > C or breast ptosis grade 2/3, resulting in a larger breast or larger footprint of the breast, and edema was reported (OR 5.34 95% CI 1.2-24.12), as well as a significant association between 1L increase in breast volume and edema (OR 3.65 95% CI 2.54-5.24) (Table 7 and 9) (17). Also a larger breast size was independently associated with more toxicity in two studies,

though different cut-off values were used: breast size >1500cm^3 (OR 2.10 95% CI 1.03-4.30) and breast size >1032cm^3 (OR 1.01 95% CI 1.00-1.03) (27,29). No association between breast size and late radiation toxicity was seen in 7/13 studies (Supplementary material B-E). Also, the results for the association between tumor location, body mass index (BMI) and diabetes mellitus with late radiation toxicity were contradictory in several studies (Supplementary material B).

Other factors associated with late radiation toxicity

A significant association between grade 1 general radiation toxicity and tobacco smoking was reported in one study (OR 2.15 95% CI 1.38-3.34) (Table 4) (32). The same study also found a significant association between 3DCRT in comparison to accelerated hypofractionated radiotherapy technique (reported as MARA-1) and respectively grade 1 and grade 2 general radiation toxicity (OR 2.18 95% CI 1.50-3.18 and 3.01 95%CI 1.08-8.42). One retrospective study found a favorable association between increasing tumor grade and fibrosis (OR grade 2 vs. 1 0.54 (95% CI 0.29-0.99); grade 3 vs. 1 0.29 (95% CI 0.11-0.74)) (Table 6) (19).

Discussion

The purpose of this systematic review was to provide an overview of factors associated with late radiation-induced breast toxicity after post-operative whole breast external beam irradiation in the modern 3D radiotherapy era. It is important to take factors associated with late radiation toxicity into account in order to evaluate new radiotherapy techniques. To our knowledge, no previous overview or systematic review was published on this topic. A higher radiotherapy dose or increased radiotherapy volume was associated with more late local radiation toxicity, as well as additional radiotherapy boost on the tumor bed. There was a wide variation in the way individual factors were defined and in the results of the studies included in this review. Due to heterogeneity of the data, high quality evidence for factors associated with late radiation toxicity in breast cancer patients is therefore still lacking.

However, inconsistency between studies and study results made interpretation for this review difficult. The definition and measurement of determinants differed per study. For example, increased radiotherapy volume was defined as: increased radiotherapy volume measured (continuous), increase of volume per 10cm^3,

increase PTV or CTV volume in different studies. Although we could conclude that increased radiotherapy dose or irradiated volume resulted in more toxicity, it was therefore difficult to draw other conclusions, such as a definite volume parameter, from these results. Also, the given breast cancer treatment varied per study. In some studies, all patients received a boost whereas in other studies no boost was given. Furthermore, in most studies patients were treated with breast conserving surgery and in some studies part of the study population was treated with mastectomy. Finally, there was a lot of variation in the study results. Especially in the category patient characteristics, factors - such as age - could be significantly associated with late radiation toxicity in one study and not significant in another study. The heterogeneity of the results might be caused by several factors. First, different grading systems for late radiation toxicity were used in the included studies (e.g., RTOG criteria, CTCAE criteria, LENT-SOMA scale). As the selected outcome method varies between the studies, the determinants associated with the outcome may also vary between studies. Second, the selection criteria of some cohort studies varied. For example the study of Bergom et al. only included patients with large breasts, the study of Meattini et al. only included patients < 60 years old, while the study of La Rocca et al. only included patients > 65 years old (19,21,28). Consequently, the conclusions on patient characteristics might vary per study, as the accrued patient population also varied.

The methodology of the included studies caused some limitations. The way studies handled missing data was not reported in the majority of the studies. If no imputation method was used and missing cases were omitted in the analysis, there is a risk of selection bias, which could influence the outcome. Therefore, all these studies scored a high risk of bias. Their results should be interpreted with caution. Also, there were 7/21 studies with a retrospective design, leading to a risk of bias. Patients with co-morbidities or post-operative complications might have more extensive follow-up or patient files than patients without co-morbidities or complications. As a consequence, their reports on late radiation toxicity could also be different. For example in the study of Meattini et al. where a higher tumor grade was associated with less toxicity (19). However, breast cancer patients with a grade 3 tumor receive no additional boost, in contrast to patients with grade 1-2. Potentially, toxicity was not caused by lower tumor grade, but due to the absence of tumor bed boost, as adjustment for tumor boost was not performed.

Radiotherapy treatment has evolved greatly over the past decade. Hypofractionated radiotherapy has become the standard treatment in many countries, as different studies showed that it is a safe treatment option without increased toxicity in comparison to standard fractionation (8,41,42). For example in the START A trial 2236 breast cancer patients were randomized to receive 41.6 Gy (13 fractions), 39.0 Gy (13 fractions) or 50 Gy (25 fractions, control group) (43). After median follow-up of 5 years, there was a trend toward less patient reported toxicity (i.e., breast shrinkage, breast hardness and swelling of the affected breast) in the groups receiving 41.6 Gy and 39.0 Gy in comparison to 50 Gy. However, no significant association between patient reported toxicity and radiotherapy was seen. Significant less physician reported breast induration and breast edema was seen in the group receiving 39 Gy in comparison to 50 Gy at 10 year follow up (8). In the START B trial, 2215 breast cancer patients were randomly assigned to receive 50 Gy in 25 fractions (control) or 40 Gy in 15 fractions (intervention) (44). Again, a (non-significant) trend towards less patient reported toxicity was seen in the group receiving a lower radiotherapy dose. However, at 10 years follow-up significant less breast shrinkage and breast edema was seen in the group receiving 40 Gy in comparison to the group receiving 50 Gy (8). As a result, hypofractionated radiotherapy is implemented and part of standard care in the Netherlands. Simultaneously, new radiotherapy techniques, such as ultra-hypofractionation (i.e., 5 fractions) are developed, resulting in similar or lower toxicity rates (9,45). Also, partial breast irradiation is an upcoming treatment modality for patients with low-risk breast cancer. In the randomized IMPORT LOW study, partial breast radiotherapy resulted in significant less adverse events (incidence rate ratio 0.77), such as breast appearance, in comparison to 40 Gy whole-breast radiotherapy (46). Also, patient reported breast appearance 5 years after radiotherapy was significantly better in the partial breast irradiation group (HR .064 95% CI 0.46-0.89) and reduced radiotherapy dose group (HR 0.74 95% CI 0.54-1.00) in contrast to whole breast group irradiated with 40 Gy (47). In the Florence trial, patients were randomized to receive accelerated partial breast irradiation with IMRT or whole breast irradiation with 2D-RT (48). The cosmetic outcome was significantly better in the partial irradiated group in contrast to whole breast irradiation (p 0.045). Also, less late radiation toxicity (any grade, using RTOG criteria) was reported in the partial breast group (p 0.004). However, as these trials are randomized trials, no patient- or treatment related factors associated with late radiation toxicity were evaluated, and they were not included in our systematic review.

In the modern treatment area, like in 2D radiotherapy, increased radiotherapy dose and volume are associated with late radiation toxicity. We need to further explore if treatment adaptation and early intervention can prevent late radiation toxicity and knowing the factors that might induce late radiation toxicity, the possibility of individual treatment adaptation could be investigated and the effect of early intervention to prevent or reduce the risk of late radiation toxicity could be evaluated. Also, the optimal treatment for late radiation toxicity in breast cancer patients needs to be investigated.

Conclusion

Increased radiotherapy dose, including boost, or increased radiotherapy volume is associated with more late radiation toxicity after whole breast irradiation in the modern treatment era. It is important to further reduce late radiation toxicity rates without compromising locoregional control and survival, using treatment de-escalation such as partial breast irradiation patients receive a smaller total radiotherapy dose and selected use of tumor bed boost.

Supplementary material

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Patient-reported symptoms of late radiation toxicity in breast cancer patients and the association with quality of life

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Submitted

Abstract

Purpose: Assess the prevalence of patient-reported symptoms of local late radiation toxicity (LRT) in breast cancer patients and determine the association between LRT and quality of life.

Methods: Within the prospective UMBRELLA cohort, a survey on self-reported LRT was sent to all breast cancer patients with ≥ 12 months interval since radiotherapy treated with curative intent. Symptoms of LRT were evaluated on a 4-point Likert scale. LRT was defined as grade 3-4 (moderate-severe) breast or chest-wall pain combined with at least one other grade 2-4 (mild-severe) LRT symptom, i.e., breast or arm/hand lymphedema, firmness of the breast or impaired arm movement. Physical, role (i.e., impairment occupational or family role) and social functioning were measured before, during, and after the LRT survey using the EORTC QLQ C30 and compared to a Dutch normative population.

Results: 1661/2236 patients (74%) responded to the LRT survey. Of those, 16% (*n* = 273) reported LRT. The median cohort follow-up was 38 months (range 12-90). Moderate/severe firmness of the breast and moderate/severe chest-wall and breast pain were reported by 19% (*n* = 316), 14% (*n* = 233) and 10% (*n* = 166) patients, respectively. Physical, role and social functioning was below the clinical threshold (i.e., clinically relevant impairment) in 21-47% of patients with LR and 4-20% of patients without LR. Patients with self-reported LRT significantly more often received analgesics, physiotherapy and lymphedema therapy compared to patients without LRT.

Conclusion: This study provided insight into the prevalence of LRT and the influence of LRT on quality of life and functioning after breast cancer. Knowing the expected long-term effects of breast cancer treatment may help patients and physicians to outweigh the clinical benefits of radiotherapy against the expected late radiation toxicity side effects.

Introduction

Postoperative radiotherapy plays an important role in breast cancer treatment: it reduces the risk of locoregional recurrence and improves survival (1,2). However, postoperative radiotherapy also increases the risk of local late radiation toxicity (LRT), which is characterized by pain, firmness of the breast, lymphedema of the breast and arm, impaired cosmetic results and impaired mobility of the arm (3–6). The Common Terminology Criteria for Adverse Events (CTCAE) and the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) are the most commonly used standards by radiation oncologists for evaluating late radiation toxicity (7,8). However, little is known about patient-reported symptoms of late radiation toxicity and the impact of self-reported symptoms of late radiation toxicity on quality of life (QoL).

The aim of this study was to assess the prevalence of patient-reported symptoms of late radiation toxicity in a large prospective cohort of women (being) treated for breast cancer. In addition, we evaluated the association between patient-reported symptoms of late radiation toxicity and different domains of quality of life.

Methods

This study was conducted within the prospective observational multicenter 'Utrecht cohort for multiple breast cancer intervention studies and long-term evaluation' (UMBRELLA) (9,10). Since 2013, the UMBRELLA study included patients ≥ 18 years old, with histologically proven invasive breast cancer or ductal carcinoma in situ (DCIS) referred to the department of Radiation Oncology of the University Medical Center Utrecht for postoperative radiation therapy. Other inclusion criteria were good understanding of the Dutch language and no mental impairment. Only patients with at least one year follow-up were included in the present study in order to select patients who finished primary systemic treatment (i.e., chemotherapy and/or HER2 targeted therapy). Another reason to include patients > 1 year follow-up is the fact that it takes time for LRT to develop. The UMBRELLA study adheres to the Dutch Law on Medical Research Involving Human Subjects (WMO) and the Declaration of Helsinki (version 2013). Ethical approval was obtained from the Medical Ethical Committee of the University Medical Center Utrecht (NL52651.041.15, Medical Ethics Committee 18/399). All patients

consented for the re-use of their clinical data and patient reported outcome measurements (PROMs). Within UMBRELLA, tumor and treatment characteristics are provided by the Netherlands Comprehensive Cancer Organization (IKNL). Smoking and body mass index (BMI) were collected within the context of the cohort study. Participants who smoked during follow-up in UMBRELLA were classified as active smokers. BMI was calculated as weight / height^2.

Between October 2019 and December 2020, eligible patients were invited to complete an extra survey on self-reported symptoms of local late radiation toxicity. Non-respondents received a reminder after one month. The survey included nine questions of several domains of the cancer specific Quality of Life Core Questionnaire (QLQ C30) and the breast cancer-specific questionnaire (QLQ BR23) of the European Organization for Research and Treatment of Cancer (EORTC), i.e., physical, functioning, role functioning (i.e., functioning in your role around family, friends or in an occupational environment), and social functioning (11,12). To estimate the prevalence of LRT, ten additional questions were developed by a radiation oncologist, surgeon, epidemiologist, and hyperbaric oxygen physician. These questions were based on the Common Terminology Criteria for Adverse Events (CTCAE version 4), the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the EORTC QLQ C30 and QLQ BR23 and evaluated to what extent patients experienced breast / chest-wall pain, arm / shoulder pain, firmness of the breast, breast and arm / hand lymphedema, impaired arm movement and satisfaction with cosmetic outcome (7,8,11,12). All questions were scored on a 4-point Likert scale, i.e., “not at all”, “a little”, “quite a bit” and “very much”. Patients were classified as having late radiation toxicity when they reported grade 3 or 4 (moderate to severe) breast or chest-wall pain in combination with at least one other grade 2-4 (mild to severe) LRT symptom, i.e., breast or arm/hand lymphedema, firmness of the breast and / or impaired arm movement.

In the longitudinal UMBRELLA cohort, patient reported outcomes were collected at regular intervals during and after treatment (i.e., before the start of radiation therapy (after surgery [baseline]), after 3 and 6 months, and each 6 months up to 10 years thereafter) (9). The late radiation toxicity questionnaire was sent in between two standard UMBRELLA cohort questionnaires. Quality of life outcomes, collected by the extra late radiation toxicity questionnaire (T0), were compared to

similar outcomes collected by regular UMBRELLA cohort questionnaires prior to (T-1) and after the extra questionnaire (T+1).

Statistics

Frequencies with proportions, means with ranges or standard deviations for normally distributed variables and medians with interquartile ranges for skewed data were used for descriptive statistics. Sum scores for the EORTC (ranging from 0 to 100) were calculated in accordance with the EORTC scoring manual (13). Thresholds for clinical importance were used to evaluate the proportion of patients that experience clinically relevant impairment in the different quality of life domains (resp., 83, 58 and 58 for physical, role and social functioning) (14). EORTC QoL outcomes of the study population were compared to those of a Dutch normative population (*n* = 860), consisting of women with a comparable age to our study population, who never had been diagnosed with cancer (15). Statistical analyses were performed with IBM Statistical Package for Social Sciences (SPSS) software, version 25.

Results

Of the 3470 patients included in UMBRELLA by December 2020, 2233 patients were eligible for present study (Supplementary Figure 1). Of those, 1661 patients (74%) responded to the questionnaire. The median age was 58 (range 24-84) and 99.6% (*n* = 1654) of the patients were female (Table 1). Most patients (*n* = 1327, 80%) were treated with lumpectomy (Table 1). All patients received some type of radiotherapy. The majority of the patients received local radiotherapy either with boost (*n* = 496, 30%) or without boost (*n* = 617, 37%). The median follow-up was 38 months (range 12-90 months). Non-responders were on average younger (median 53 vs. 58 years, resp.) and less often received lumpectomy (72% vs. 80%, resp.) and local radiotherapy with boost (23% vs. 30%, resp.), in comparison to responders (Supplementary table 1).

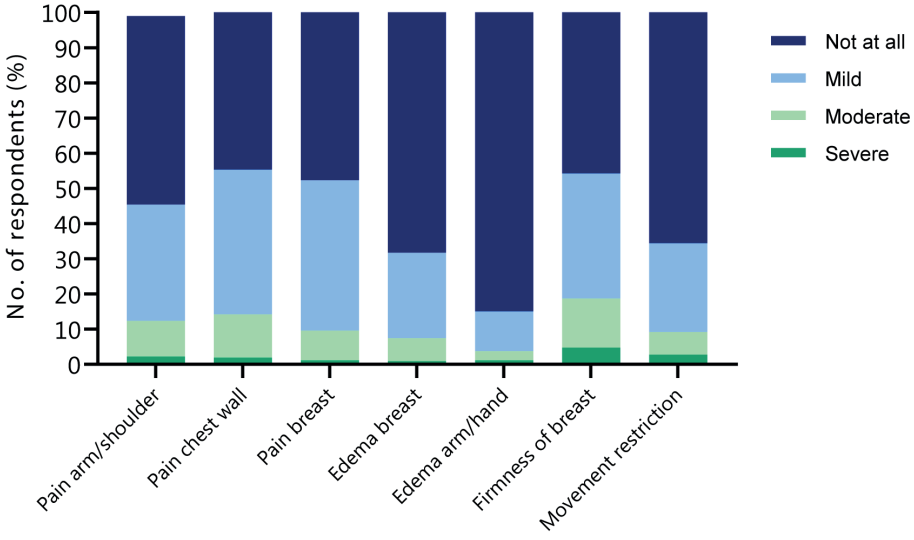
Table 1. Patient, tumor and treatment characteristics of irradiated breast cancer patients in the UMBRELLA cohort study with > 12 months follow-up.

	***n* = 1661**
Sex [*n* (%)]	
Female	1654 (99.6)
Male	7 (0.4)
Age at cohort enrolment [median (range)]	58 (24-86)
Pathological T stadium [*n* (%)]	
0 + In situ (IS)	264 (15.9)
I	936 (56.4)
II	336 (20.2)
III-IV	38 (2.3)
X + unknown	87 (5.2)
Type of surgery	
Lumpectomy	1327 (79.9)
Mastectomy	164 (9.9)
Mastectomy with direct breast reconstruction	115 (6.9)
Unknown	55 (3.4)
Axillary treatment	
Sentinel node procedurea	1308 (78.7)
Axillary lymph node dissection	143 (8.6)
No axillary treatment	146 (8.8)
Unknown	16 (2.1)
Systemic treatment[b]	
Chemotherapy	679 (41.8)
Hormonal therapy	785 (48.3)
HER2-targeted therapy	188 (11.6)
No systemic treatment	628 (37.8)
Unknown	37 (2.2)
Radiotherapy treatment	
Partial breast irradiation	23 (1.4)
Local radiotherapy without boost	617 (37.1)
Local radiotherapy with boost	496 (29.9)
Locoregional radiotherapy without boost[c]	237 (14.3)
Locoregional radiotherapy with boost[c]	150 (9.0)
Unknown	138 (8.3)
Smoking	
Active smoker [d]	163 (9.8)
Former smoker	713 (42.9)
Non-smoker	691 (41.6)
Unknown	94 (5.7)
BMI [median (IQR)][e]	25.6 (5.7)
Unknown [*n* (%)]	64 (4)
Follow-up (months) [median (range)]	38 (12-90)

Unless stated otherwise, numbers are shown as *n* (%). Categories may not sum to a total of 100% due to rounding. Abbreviations: IQR= interquartile range;
[a] Including MARI / targeted axillary dissection procedure [b] Total percentage > 100% as patients may receive a combination of systemic treatment. [c] Radiation therapy on periclavicular and / or axillary lymph nodes [d] Active smoking during cohort participation [e] Calculated as weight / height^2

Symptoms of skin and subcutaneous tissue toxicity were: 19% (*n* = 316) of all patients reported moderate to severe breast firmness, 14% (*n* = 233) reported moderate to severe chest wall pain (i.e., musculoskeletal pain) and 10% (*n* = 166) moderate to severe pain in the breast (Figure 1). Of all patients, 3% (*n* = 50) reported moderate to severe lymphedema of the arm or hand. Overall, 273 (16%) patients were classified as having self-reported late radiation toxicity. Of all patients with self-reported LRT, respectively 80% (*n* = 218) and 57% (*n* = 156) reported moderate to severe chest-wall and breast pain in contrast to 1% (*n* = 14) and 0.4% (*n* = 6) in the group of patients classified as no self-reported LRT (Supplementary figure 2). In total, 60% (*n* = 164) of all patients with LRT reported moderate to severe symptoms of firmness of the breast in comparison to 10% of the patients classified as no self-reported LRT.

Figure 1. Prevalence of self-reported symptoms of late radiation toxicity in breast cancer patients.



Patients with self-reported LRT received analgesics, physiotherapy and lymphedema therapy 2-8 times more often in comparison to patients without self-reported LRT (Table 2). The most common therapy to alleviate symptoms of LRT was lymphedema therapy, which was reported by 56% of the patients with LRT. Patients with LRT were on average younger (53 vs. 58 years, resp., Table 3), more often received chemotherapy (54% vs. 38%, resp.) in comparison to patients without LRT and more often received ablative surgery with or without immediate

breast reconstruction (73% vs. 81%, resp.). Patients with LRT were on average more often treated with radiotherapy boost (44% vs. 38%, resp.) and locoregional radiotherapy (30% vs. 22%, resp.) in comparison to patients without LRT.

Table 2. Proportion of breast cancer patients with and without self-reported late radiation toxicity receiving care aimed at reducing LRT.

	With self-reported LRT *n* = 273	**Without self-reported LRT** *n* = 1388	**Total** *n* = 1661
Analgesics	44 (16.2)	30 (2.2)	74 (4.5)
Physiotherapy	98 (36.0)	211 (15.3)	309 (18.7)
Lymphedema therapy	152 (56.1)	304 (22.0)	456 (27.6)
HBOT	11 (4.1)	9 (0.7)	20 (1.2)
Any treatment[a]	195 (71.7)	527 (38.1)	722 (43.7)

Abbreviations: LRT = late radiation toxicity, HBOT = hyperbaric oxygen therapy
Late radiation toxicity is defined as grade 3 or 4 (moderate to severe) breast or chest-wall pain in combination with at least one other grade 2 to 4 (mild to severe) LRT symptom, i.e., breast or arm / hand lymphedema, firmness of the breast and/or impaired arm movement.
[a] Any treatment aiming at reducing LRT (i.e., analgesics, physiotherapy, lymphedema therapy and / or HBOT).

Table 3. Patient- treatment and tumor characteristics of breast cancer patients with and without self-reported late radiation toxicity.

	Late radiation toxicity *n* = 273	**No late radiation toxicity** *n* = 1388
Sex [*n* (%)]		
Female	272 (16.4)	1382 (83.6)
Male	1 (14.3)	6 (85.7)
Age at cohort enrolment [median (range)]	53 (26-81)	58 (24-86)
Pathological T stadium [*n* (%)]		
0 + In situ (IS)	50 (18.3)	214 (15.4)
I	132 (48.4)	804 (57.9)
II	69 (25.3)	267 (19.2)
III-IV	9 (3.3)	29 (2.1)
X + unknown	13 (4.8)	74 (5.3)
Type of surgery		
Lumpectomy	199 (72.9)	1128 (81.3)
Mastectomy	34 (12.5)	130 (9.4)
Mastectomy with direct breast reconstruction	29 (10.6)	86 (6.2)
Unknown	11 (4.0)	43 (3.1)
Axillary treatment		
Sentinel node procedure[a]	218 (79.9)	1090 (78.5)
Axillary lymph node dissection	26 (9.5)	117 (8.4)
No axillary treatment	19 (7.0)	127 (9.1)
Unknown	10 (3.7)	54 (3.9)

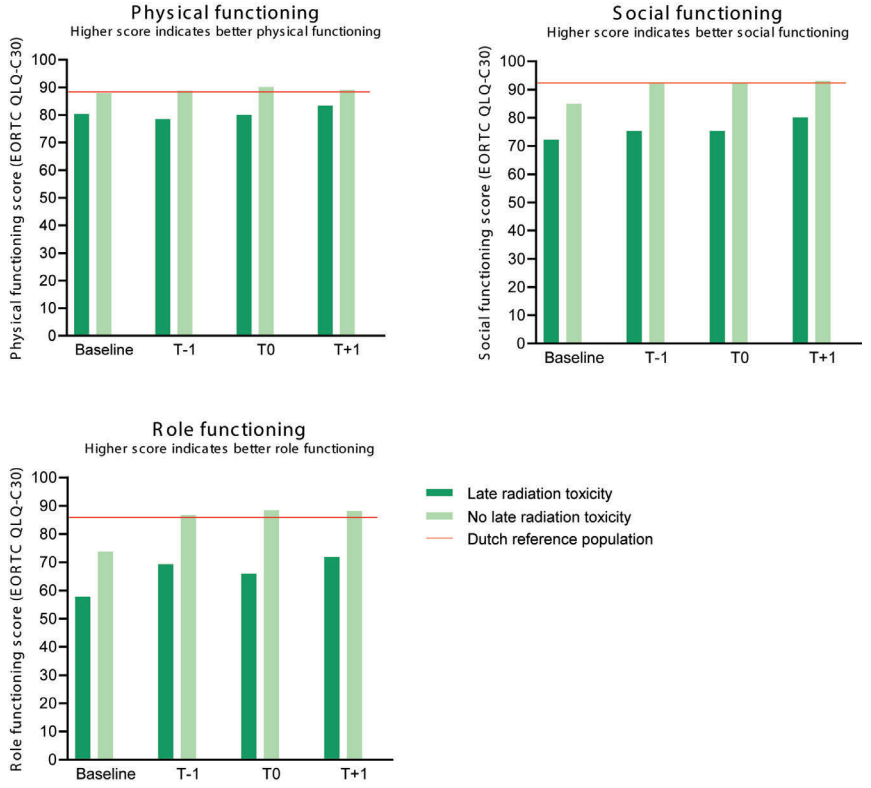
Systemic treatment[b]		
Chemotherapy	148 (54.2)	531 (38.3)
Hormonal therapy	132 (48.4)	653 (47.0)
HER2-targeted therapy	43 (15.8)	145 (10.4)
No systemic treatment	76 (27.8)	552 (39.8)
Radiotherapy boost		
Radiotherapy with boost	121 (44.3)	525 (37.8)
Radiotherapy without boost	126 (46.2)	751 (54.1)
Unknown	26 (9.5)	112 (8.1)
Radiotherapy target volumes		
Local[c]	166 (60.8)	970 (69.9)
Locoregional[d]	81 (29.7)	306 (22.0)
Unknown	26 (9.5)	112 (8.1)
Smoking		
Active smoker[e]	37 (13.6)	126 (9.1)
Former smoker	114 (41.8)	599 (43.2)
Non-smoker	102 (37.4)	589 (42.4)
Unknown	20 (7.3)	74 (5.3)
BMI [median (IQR)][f]	26.7 (5.7)	25.4 (5.7)
Unknown [*n* (%)]	10 (8)	34 (5)
Follow-up (months) [median (range)]	37 (13-85)	38 (12-90)

Unless stated otherwise, numbers are shown as *n* (%). Categories may not sum to a total of 100% due to rounding. Late radiation toxicity is defined as grade 3 or 4 (moderate to severe) breast or chest-wall pain in combination with at least one other grade 2 to 4 (mild to severe) LRT symptom, i.e., breast or arm/hand lymphedema, firmness of the breast and/or impaired arm movement. Abbreviations: IQR = interquartile range; SD = standard deviation
[a] Including MARI procedure / targeted axillary dissection procedure [b] Total percentage > 100% as patients may receive a combination of systemic treatment. [c] Including patients treated with partial breast irradiation (*n* = 23). [d] Radiation therapy on periclavicular and / or axillary lymph nodes. [e] Active smoking during UMBRELLA cohort participation [f] Calculated as weight / height^2

Almost half of the patients with LRT scored below the clinical threshold for physical functioning before, during and after the late radiation toxicity questionnaire (33-52%, Figure 2). The proportion of patients without LRT that scored below the clinical threshold for physical functioning (18-26%) was similar to the normative population (22%) at all four time points. At all time-points, the proportion of patients with LRT that scored below the clinical threshold for role functioning was higher in comparison to patients without LRT (22-46% and 6-23%, resp.). The proportions of patients with and without LRT that scored below the clinical threshold for role functioning were highest at baseline (46% and 23%, resp.) in comparison to the normative population (9%). Patients with LRT more often scored below the clinical threshold for social functioning at all four time points (11-24%) in comparison to patients without LRT (2-10%) and the normative population (4%). In addition,

mean EORTC scores for physical, role and social functioning were lower, indicating lower functioning, for patients with LRT in comparison to patients without LRT and the normative population (Supplementary Figure 3).

Figure 2. Proportion of breast cancer patients with and without self-reported symptoms of late radiation toxicity who function below the clinical relevant EORTC QLQ C30 thresholds immediately after surgery (i.e., baseline), prior to, during and after the late radiation toxicity questionnaire in comparison to a Dutch normative population.



Time: Baseline = upon cohort inclusion; T-1 = standard UMBRELLA cohort questionnaire before the late radiation toxicity questionnaire; T0 = at the moment of the late radiation toxicity questionnaire; T+1 = standard UMBRELLA cohort questionnaire after the late radiation toxicity questionnaire

The Dutch normative population comprised 860 women without any cancer diagnosis with comparable age to our study population. Clinically relevant thresholds, i.e., based on Giesinger et al., for the EORTC QLQ C30 domains are 83 for physical functioning, 58 for social functioning and 58 for role functioning (14).

Discussion

Patient-reported symptoms of late radiation toxicity are relatively common (i.e., 16%) after breast cancer treatment. This proportion is comparable to the START A and START B trials, in which patients received similar radiotherapy in comparison to our study. After 5 years follow-up 7.1-18.9% of the patients reported moderate or marked normal tissue toxicity (i.e., breast induration, breast or arm edema or shoulder stiffness) (16). In our study, patients with self-reported late radiation toxicity scored lower in terms of physical, role and social functioning in comparison to patients without late radiation toxicity. In the group of patients with self-reported late radiation toxicity, almost half of the patients scored below the clinical threshold for physical functioning. The number of patients scoring below the clinical threshold for social and role functioning was 2-3 times higher in comparison to patients without late radiation toxicity. Interestingly, patients with symptoms of late radiation toxicity already reported lower physical, role and social functioning shortly after breast cancer surgery and prior to radiation therapy. On average, patients with late radiation toxicity were younger and received a more comprehensive treatment: chemotherapy, mastectomy, and radiotherapy boost or locoregional radiotherapy.

Depending on the symptoms, late radiation toxicity can be treated with analgesics, physiotherapy, lymphedema therapy or hyperbaric oxygen therapy. However, these treatments can be time-consuming, a burden for patients and might not always be effective (17–19). For example, treatment for lymphedema often requires repetitive physical therapy and does not always resolve the symptoms (18,20). Therefore, it is important to prevent late radiation toxicity, potentially by individualizing radiotherapy treatment based on risk factors (i.e., patient and treatment characteristics) for late radiation toxicity. For that reason, it is important to know which determinants are associated with late radiation toxicity. In the present study, we observed an association between radiation boost on the tumor bed and late radiation toxicity. These findings are in line with the “boost-no boost” study, where 5569 patients were randomized after whole breast irradiation (25x2 Gy) to receive a 10-16 Gy sequential boost in the intervention group or no boost in the control group (21). In the prospective cohort study of Keller et al, 946 patients received median 46 Gy with inversed planned IMRT (22). Both studies reported that an increased boost dose, larger clinical target volume and higher boost

energy were all significantly associated with more late radiation toxicity. In the UK Standardisation of Breast Radiotherapy (START) Trial A and B, respectively 2236 and 2215 were randomized into three groups: 50 Gy in 25 fractions over 5 weeks or 41.6 Gy or 39 Gy in 13 fractions over 5 weeks. Moderate or marked breast induration, breast shrinkage, breast edema and telangiectasia were significantly less common normal tissue effects in patients receiving hypofractionated radiotherapy (23,24). These studies emphasize the importance of treatment de-escalation, such as the implementation of partial breast irradiation in low-risk breast cancer patients or (ultra-)hypofractionation including a reduced total radiotherapy dose, which results in less or equal toxicity after radiotherapy (25,26).

This study showed that patients with self-reported late radiation toxicity already had lower physical functioning prior to the start of radiation therapy in comparison to patients without late radiation toxicity. Potentially, other breast cancer treatments (i.e., surgery, chemotherapy and/or endocrine therapy) also induce LRT-like symptoms, such as breast pain, firmness of the breast and lymphedema. With the multidisciplinary treatment approach, it is impossible to determine the exact origin of the toxicity. The majority of patients with late radiation toxicity received physical therapy, lymphedema therapy or analgesics, whereas only 38% received no additional treatment. Therefore, early and longitudinal monitoring of physical functioning is important for this group of patients at risk for maintaining decreased physical functioning throughout follow-up to improve personalized (long-term) care. In addition, late radiation toxicity was associated with worse social and role functioning. Possibly, patients with late radiation toxicity are more reserved regarding social interaction. Attention for psychosocial support for these patients could be taken throughout and after the course of treatment. The results of this study provide an insight into prevalence of late radiation toxicity and their influence on the quality of life and functioning on the EORTC domains. These findings may help to adequately inform breast cancer patients about the expected long-term effects of breast cancer treatment and emphasizes the importance of shared decision making prior to breast cancer treatment, outweighing the clinical benefits of radiotherapy against the expected late radiation toxicity side effects.

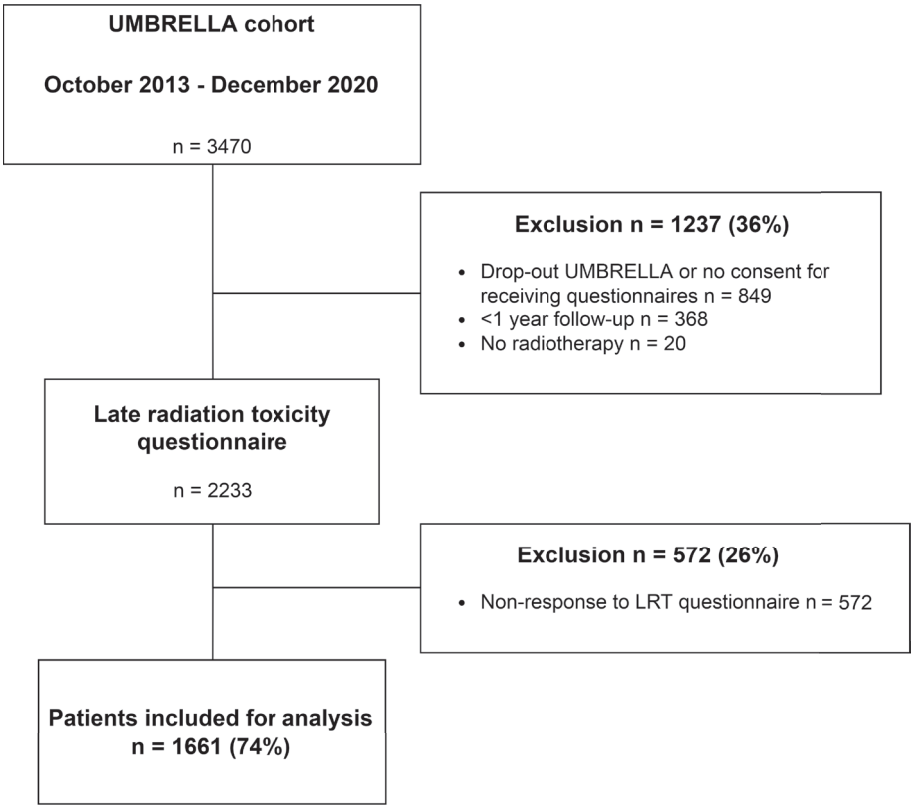
Our study suffers from some limitations. Even though the response rate was high, selective non-response cannot be ruled out. Potentially, patients that fully participate in the (longitudinal) UMBRELLA cohort, may have a higher quality of life and better physical functioning (15). Consequently, the proportion of patients

with late radiation toxicity may have been underestimated. EORTC QLQ C30 questionnaires were completed immediately after breast cancer surgery and prior to radiation therapy. Therefore, information about (breast) symptoms and quality of life prior to surgery is lacking. Consequently, it is impossible to determine if symptoms of late radiation toxicity result in lower quality of life, or if patients with lower quality of life experience a higher burden of late radiation toxicity and therefore report higher late radiation toxicity symptoms. Also, postoperative complications, such as infections, are known risk factors for the development of late radiation toxicity, but were not assessed in the present study (27). Finally, the late radiation toxicity questionnaire used for this study was sent once to all eligible patients in the cohort. Late radiation toxicity, such as fibrosis, may change over time (28). Symptoms of late radiation toxicity were only measured at one point in time in the present cross-sectional study. Therefore, the time interval for the development of late radiation toxicity, and how the self-reported symptoms of late radiation toxicity have developed over time remains unclear.

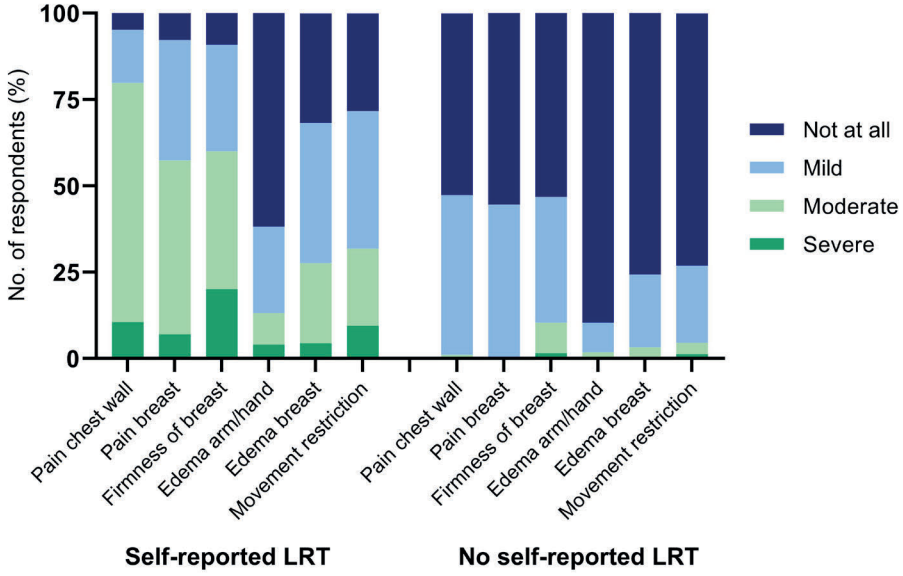
Conclusion

This study may help breast cancer physicians to inform their patients about long-term effect of breast cancer treatment. In addition, our results may support physicians and patients to outweigh the clinical benefits of radiotherapy against the expected late radiation toxicity side effects. Patient-reported symptoms of late radiation toxicity are relatively common after breast cancer treatment with a prevalence of 16%. The most common self-reported late radiation symptoms among breast cancer patients are breast and chest wall pain and firmness of the breast. Patients with self-reported symptoms of late radiation toxicity receive additional care aimed at reducing LRT, such as analgesics, physiotherapy and lymphedema therapy 2 to 8 times more often. On average, patients with late radiation toxicity were younger and received a more comprehensive treatment: chemotherapy, mastectomy and radiotherapy boost or locoregional radiotherapy. Late radiation toxicity is associated with reduced physical, role and social functioning even prior to the start of radiotherapy. The combination of treatments of breast cancer makes it impossible to determine the exact origin of the toxicity symptoms. A multidisciplinary approach to treat and reduce treatment toxicity is therefore important.

Supplementary figure 1. Flowchart of included breast cancer patients in the UMBRELLA cohort receiving the late radiation toxicity questionnaire.

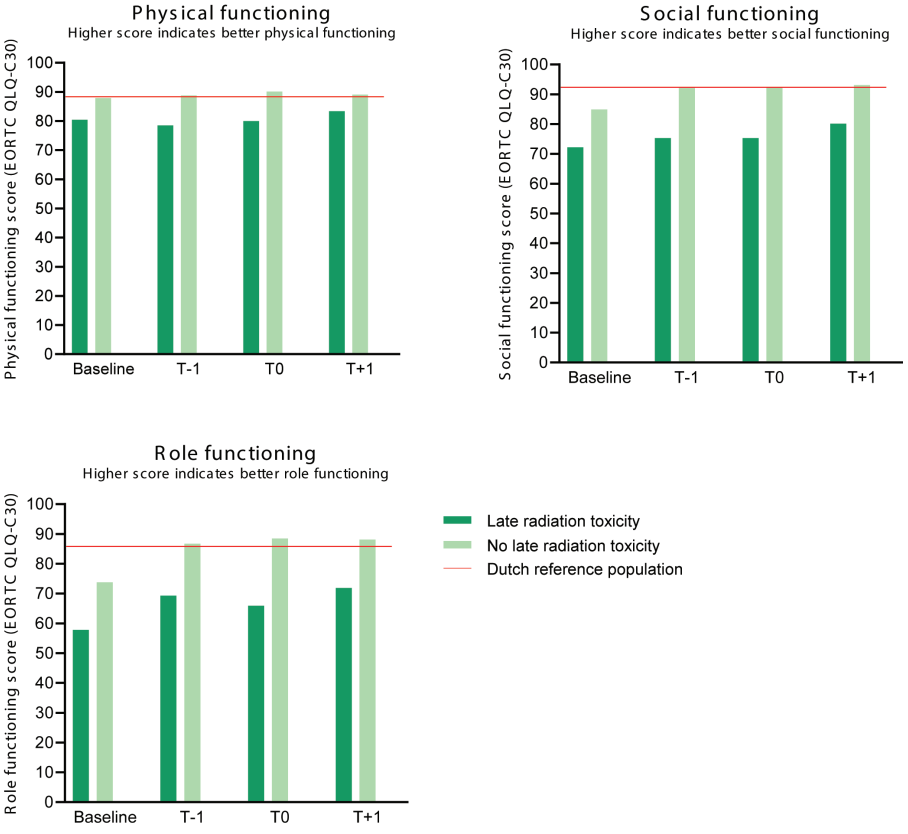


Supplementary figure 2. Prevalence of symptoms of breast cancer patients classified as self-reported late radiation toxicity in comparison to patients classified as no self-reported late radiation toxicity.



Late radiation toxicity (LRT) is defined as having grade 3 or 4 (moderate to severe) breast or chest-wall pain in combination with at least one other grade 2 to 4 (mild to severe) LRT symptom, i.e., breast or arm / hand lymphedema, firmness of the breast and / or impaired arm movement).

Supplementary figure 3. Mean EORTC QLQ C30 scores for breast cancer patients with and without self-reported symptoms of late radiation toxicity immediately after surgery (i.e., baseline), prior to, during, and after the late radiation toxicity questionnaire in comparison to a Dutch normative population.



Supplementary table 1. Patient-, treatment and tumor characteristics of breast cancer patients who responded to the late radiation toxicity questionnaire in comparison to non-responders.

	Responders to LRT questionnaire *n* = 1661	**Non-responders to LRT questionnaire** *n* = 570
Age at cohort enrolment [median (range)]	58 (24-86)	53 (24-83)
Pathological T stadium [*n* (%)]		
0 + In situ (IS)	264 (15.9)	89 (15.2)
I	936 (56.4)	326 (55.5)
II	336 (20.2)	122 (20.8)
III-IV	38 (2.3)	18 (3.0)
X + unknown	87 (5.2)	32 (5.5)
Type of surgery		
Lumpectomy	1327 (79.9)	421 (71.7)
Mastectomy	164 (9.9)	75 (12.8)
Mastectomy with direct breast reconstruction	115 (6.9)	74 (12.6)
Unknown	55 (3.4)	17 (2.9)
Axillary treatment		
Sentinel node procedure	1308 (78.7)	458 (78.0)
Axillary lymph node dissection	143 (8.6)	64 (10.9)
No axillary treatment	146 (8.8)	47 (8.0)
Unknown	16 (2.1)	18 (3.1)
Systemic treatment[a]		
Chemotherapy	679 (41.8)	277 (47.2)
Hormonal therapy	785 (48.3)	288 (49.1)
HER2-targeted therapy	188 (11.6)	75 (12.8)
No systemic treatment	628 (37.8)	186 (31.7)
Unknown	37 (2.2)	4 (0.7)
Radiotherapy treatment		
Partial breast irradiation	23 (1.4)	4 (0.7)
Local radiotherapy without boost	617 (37.1)	197 (33.6)
Local radiotherapy with boost	496 (29.9)	134 (22.8)
Locoregional radiotherapy without boost[b]	237 (14.3)	92 (15.7)
Locoregional radiotherapy with boost[b]	150 (9.0)	58 (9.9)
Unknown	138 (8.3)	102 (17.4)
Smoking		
Active smoker[c]	163 (9.8)	71 (12.1)[d]
Former smoker	713 (42.9)	212 (36.1)[d]
Nonsmoker	691 (41.6)	153 (26.1)[d]
Unknown	94 (5.7)	151 (25.7)
BMI (median [IQR])[d]	25.6 (5.7)	25.8 (6.5)
Unknown [*n* (%)]	64 (4)	213 (36.3)
Follow-up (months) [median (range)]	38 (12-90)	42 (12-86)

Unless stated otherwise, numbers are shown as *n* (%). Categories may not sum to a total of 100% due to rounding. [a] Total percentage > 100% as patients may receive a combination of systemic treatment. [b] Including radiation therapy on periclavicular and / or axillary lymph nodes. [c] Active smoking during follow-up [d] Valid proportion is shown [d] Calculated as weight / height^2

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6

The impact of hyperbaric oxygen therapy on late radiation toxicity and quality of life in breast cancer patients

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Abstract

Purpose: To evaluate symptoms of late radiation toxicity, side effects and quality of life in breast cancer patients treated with hyperbaric oxygen therapy (HBOT).

Methods: Cohort study of breast cancer patients treated with HBOT in 5 Dutch facilities. Breast cancer patients with late radiation toxicity treated with ≥ 20 HBOT sessions from 2015 to 2019 were included. Breast and arm symptoms, pain and quality of life were assessed by means of the EORTC QLQ C30 and BR23 before, immediately after, and 3 months after HBOT on a scale of 0 to 100. Determinants associated with persistent breast pain after HBOT were assessed.

Results: 1005/1280 patients were included for analysis. Pain scores decreased significantly from 43.4 before HBOT to 29.7 after 3 months ($p < 0.001$). Breast symptoms decreased significantly from 44.6 at baseline to 28.9 at 3 months follow-up ($p < 0.001$) and arm symptoms decreased significantly from 38.2 at baseline to 27.4 at 3 months follow-up ($p < 0.001$). All quality of life domains improved at the end of HBOT and after 3 months follow-up in comparison to baseline scores. Most prevalent side effects of HBOT were myopia (any grade, $n = 576$, 57.3%) and mild barotrauma ($n = 179$, 17.8%). Moderate / severe side effects were reported in 3.2% ($n = 32$) of the patients. Active smoking during HBOT and shorter time (i.e., median 17.5 vs. 22.0 months) since radiotherapy were associated with persistent breast pain after HBOT.

Conclusion: Breast cancer patients with late radiation toxicity reported reduced pain, breast and arm symptoms and improved quality of life following treatment with HBOT.

Key words: breast cancer, radiation toxicity, hyperbaric oxygen therapy, quality of life

Introduction

Around 68% of all women with breast cancer undergo radiotherapy as part of their treatment (1). Even though radiotherapy techniques have improved over time, it still may – in combination with systemic therapy and surgery – induce late radiation toxicity (2–4). Late radiation toxicity is characterized by a combination of breast or chest wall pain, breast and / or arm edema, fibrosis, impaired arm movement, telangiectasia and impaired cosmetic outcome after radiotherapy. Symptoms such as fibrosis and breast pain may continue to increase during at least 10 years after radiotherapy and substantially impair daily functioning and quality of life (5).

Treatment of late radiation toxicity depends on the symptoms and may consist of analgesics, physiotherapy, lymphedema therapy and in some cases (reconstructive) surgery. Another proposed treatment for late radiation toxicity hyperbaric oxygen therapy (HBOT). During HBOT patients inhale 100% oxygen in a hyperbaric chamber with increased air pressure. The combination of oxygen and increased air pressure induces neovascularization and stimulates formation of collagen by fibroblasts (6,7). HBOT has been proven a safe and effective treatment for late radiation toxicity in different tumor sites (8–10). For that reason, HBOT for late radiation toxicity is endorsed by insurers in the Netherlands. However, evidence for the effectivity of HBOT in breast cancer patients with late radiation toxicity is limited (11,12). Consequently, in the Netherlands, HBOT is mostly used as a treatment option for late radiation toxicity in breast cancer patients who insufficiently benefitted from analgesics, physiotherapy or lymphedema therapy.

The aim of this cohort study was to evaluate patient reported late radiation toxicity in breast cancer patients treated with HBOT between 2015 and 2019 in one centre providing hyperbaric oxygen therapy in the Netherlands. Secondly, side effects after HBOT, quality of life and factors associated with effectivity of treatment were assessed.

Methods

All breast cancer patients with late radiation toxicity referred between January 2015 and December 2019 for HBOT in the Institute for Hyperbaric Oxygen Therapy (IvHG) were eligible for inclusion. The IvHG has five locations in the

Netherlands. Patients who provided written consent for the use of their data for research purposes were included. Patients referred to the IvHG who were found to be ineligible for HBOT (e.g., due to comorbidities), patients treated with < 20 HBOT sessions or patients referred for re-treatment with HBOT were excluded. Also, patients with osteoradionecrosis and patients treated with HBOT prior to surgery were excluded, as they were treated with a different number of HBOT treatment sessions. Prior to HBOT, a physician confirmed late radiation toxicity and determined if the breast or chest wall symptoms (i.e., a combination of breast or chest wall pain, breast and / or arm edema, fibrosis, impaired arm movement, telangiectasia and impaired cosmetic outcome) were likely to be the result of radiotherapy. After data collection, the complete dataset was anonymized and transferred to the division of Imaging and Oncology of the UMCU to ensure independent analysis. Data analysis was performed by independent researchers of the UMCU. Staff of the IvHG had no role in study design or decision to file the manuscript for publication. The institutional review board of the University Medical Center Utrecht (UMCU) approved this study.

Hyperbaric oxygen therapy

Standard HBOT consisted of 40 treatment sessions (1 session/day, 5 days/week) at 2.5 atmospheres absolute (ATA), with a duration of 115 minutes per session (10 minutes compression, 4 times 20 minutes 100% oxygen with breaks of 5 minutes and 10 minutes decompression) (13). HBOT is administered in a high-pressure chamber. After reaching the desired treatment pressure (2.5 ATA) the patient starts breathing 100% oxygen by a closed built- in breathing system (either a hood or a mask). For safety reasons, the chamber is only filled with air under pressure and the patient always breaths oxygen by a closed system. Patients may receive more or less treatment sessions. For example, treatment effect is evaluated with the HBO physician after 30 treatment sessions. If no treatment effect was seen after 30 sessions, patients could stop HBO treatment after 30 sessions. Also, patients may receive more or less than 40 HBO sessions for other reasons related to HBO (i.e., side effects, sufficient results prior to 40 sessions) or not related to HBO (i.e., planned vacation, medical problems not related to HBO, personal circumstances). Therefore, reasons for treatment sessions other than 40 were recorded. At 3 months after the last HBO session, patients were contacted

by phone and received the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ).

Data collection

Patient, treatment and tumor characteristics, HBO treatment details and side effects were extracted from the individual patient records. Patient-reported outcome measures were collected as part of routine clinical care. All data were entered into a database by a research nurse. In accordance with a data collection protocol designed by the UMCU research team, data from the patient files were entered into a standardized case report form. Quality of data extraction was regularly monitored by comparing CRFs with the source documents (around 32 cases, 3%).

Outcome measurements

Patient-reported outcome measurements

Breast / chest wall and arm symptoms, pain, and quality of life were collected as part of standard care using the EORTC QLQ. The EORTC QLQ comprises 30 quality of life and functioning items (C30) as well as 23 breast specific items (BR23) (14). All items were scored on a 4-point Likert scale. Total scores (0 to 100) for subscales of the EORTC questionnaires were calculated using the EOTC scoring manual. For functional scales, a higher score indicated a better outcome. For symptom scales, a higher score indicated more symptoms. Breast symptoms were evaluated using four questions on pain, swelling, sensitivity and skin problems in the affected breast or chest wall (BR23). The arm symptom scale is based on 3 items: pain and swelling in arm or shoulder and difficulty to move the arm up or sideways. The EORTC QLQ questionnaires were used as part of standard treatment. Patients received questionnaires at predefined time-points, i.e., prior to treatment (baseline), after the last HBO session (2 months after baseline) and at 3 months after the last HBO session (5 months after baseline).

Cohort outcomes and side effects

Side effects of HBOT were evaluated by the HBO physician during follow-up visits (i.e., after 15, 30 and 40 sessions and by telephone at 3 months after the

end of HBOT). Side effects after HBOT may include: barotrauma, hypoglycemia, myopia, fatigue, cataract, sinus squeeze, (acute or chronic) oxygen toxicity, cardiac decompensation / heart failure, decompression disease, or pneumothorax. Otoscopy was only performed in case of ear pain or repetitive trouble equalizing middle ear pressure. Then, barotrauma was classified according to the 6-point MacFie classification (also known as modified TEED classification): no abnormalities with otoscopy (grade 0), increased vessel visibility around the eardrum (without / with minor / with major bleeding, grade 1-3), blood in middle ear (grade 4) or eardrum perforation (grade 5) (15–17). All side effects were standardly evaluated during visits with the HBOT physician. However, no grading system was available for other side effects than barotrauma. For this study, fatigue was evaluated using the EORTC QLQ C30 fatigue subscale. A fatigue score $\geq$ 71 was considered clinically relevant, based on the Thresholds for Clinical Importance of Giesinger et al. (18). Newly developed (clinically relevant) fatigue during HBOT or at follow-up was considered to be a side effect of the HBOT. Barotrauma grade 0-2, hypoglycemia, myopia and fatigue were classified as mild side effects, as they are transient in nature (19). Moderate or severe side effects were cataract, barotrauma grade 3-5, sinus squeeze, (acute or chronic) oxygen toxicity, cardiac decompensation/heart failure, decompression disease, or pneumothorax.

Statistics

Patient characteristics, breast cancer treatment, HBO treatment characteristics, and side effects were described using frequencies and proportions for categorical data and for continuous data means with standard deviation for normally distributed data and medians with interquartile ranges (IQR) were used for skewed data.

Paired T tests or Wilcoxon rank test – depending on distribution – were used to compare pain, breast symptoms, and arm symptoms between baseline (T0) and T1 (end treatment), and between T0 and T2 (follow-up), respectively. Analysis were performed using all available questionnaires. For sensitivity analysis, complete case analysis was performed. To evaluate the association between patient and treatment characteristics and persistence of breast pain after HBOT, the EORTC QLQ BR23 item on breast pain was used (item 50, “Have you had any pain in the area of your affected breast?”). Breast pain was dichotomized into moderate / severe pain and no / mild pain. Patients with persistent moderate / severe breast

pain after HBOT were categorized as unsuccessful therapy (no pain response). Descriptive statistics were used to evaluate characteristics associated with adequate treatment effect, i.e., mild or no pain at follow up. Statistical Package for Social Sciences (SPSS) software version 25 was used for analysis. A p-value < 0.05 was considered significant.

Results

Between January 2015 and December 2019, 1280 breast cancer patients were referred for HBOT. Of those, 1005 (78.5%) patients were included for analysis (Figure 1). The most common reasons for exclusion were ineligibility for HBOT (*n* = 114), treatment with < 20 HBOT sessions (*n* = 61), and no consent for the use of data for research (*n* = 46). The response rate to the EORTC questionnaire was 95% at baseline, 85% at the end of treatment, and 58% after 3 months follow-up. The majority of patients was female (*n* = 1002, 99.7%) (Table 1). The mean age was 57.9 years and most patients were treated with breast-conserving surgery (*n* = 731, 73%). The most common radiotherapy fractionation schedule was 15-19 fractions without boost (*n* = 231, 23.0%) or 21-24 fractions with boost (*n* = 176, 17.5%). In total, 336 (33.4%) patients received local radiotherapy and 264 (26.3%) patients received locoregional radiotherapy (i.e., radiation therapy on periclavicular and / or axillary lymph nodes). During HBOT, 13% (*n* = 134) of the patients were active smokers and 41% (*n* = 413) were former smokers. The time since radiotherapy ranged from 1-582 months (median 22 months). Patients who responded to all questionnaires were, on average, older (mean age 59.0 vs. 56.8) and had a longer time since radiotherapy (median 48 months vs. 37 months) than non-responders (Supplementary material Table 1).

The number of HBO sessions ranged from 20 to 60 (median 40); 73.1% (*n* = 735) of the patients received 40 HBO sessions (Table 2). Reasons for undergoing less HBOT than planned were personal circumstances (*n* = 53), sufficient results (*n* = 31), or medical problems not related to HBOT (*n* = 29). There were 32 patients that stopped HBOT early due to no or insufficient results and 17 patients that stopped due to complications of HBOT. In total, 30 patients received > 40 HBOT sessions, mostly due to disruption of treatment sessions (*n* = 13). The most common side effects of HBOT were (transient) myopia (*n* = 576, 57%), and mild barotrauma (n=179, 18%) (Table 2). Moderate / severe side effects were reported

by 32 patients: oxygen toxicity (*n* = 4, 0.4%), barotrauma grade 3-4 (*n* = 26, 2.6%), sinus squeeze (*n* = 1, 0.1%), and cataract (*n* = 1, 0.1%).

Pain scores decreased significantly from 43.4 prior to HBOT to 30.5 at the end of HBOT ($p < 0.001$), to 29.7 at 3 months follow-up ($p < 0.001$) (Figure 2). Also, a significant reduction in breast symptom scores at the end of HBOT (29.4) and 3 months follow-up (28.9) was seen in comparison to baseline score (44.6) ($p < 0.001$). Arm symptom scores reduced significantly ($p < 0.001$) from 38.2 to 26.0 at the end of treatment and 27.4 after 3 months follow-up. Repeating the analysis in the subgroup of 352 patients who completed questionnaires at all timepoints did not change the results (Supplementary table 2). Role functioning improved from 62.7 at baseline to 67.0 immediately after HBO and 73.2 after 3 months follow-up (Figure 3). Social functioning scores improved from 74.2 prior to treatment to 75.9 after treatment and further to 82.3 after 3 months follow-up. Also, emotional functioning, physical functioning and quality of life scores increased over time.

Figure 1. Flowchart of patients included for analysis after in- and exclusion criteria.

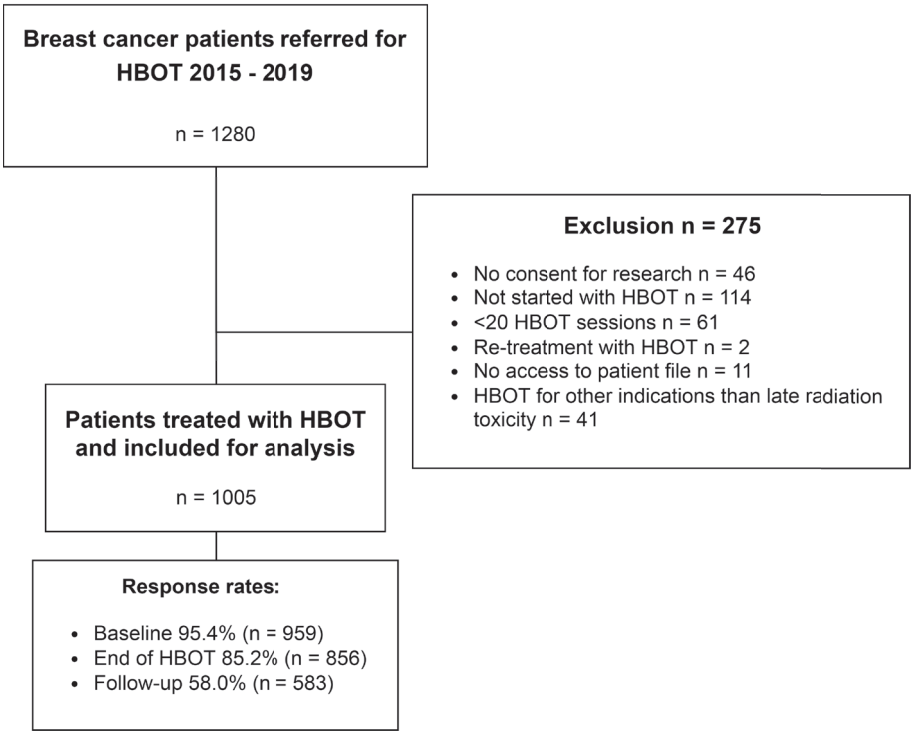


Table 1. Baseline characteristics

	***n* = 1005**
Age (mean (SD))	57.9 (9.7)
Female gender	1002 (99.7)
Pathological tumor stage[a]	
0	4 (0.4)
In situ	34 (3.4)
1	456 (45.4)
2	246 (24.5)
3	56 (5.6)
4	18 (1.8)
Unknown	191 (19)
Type of surgery	
Breast conserving surgery	731 (72.7)
Mastectomy without breast reconstruction	180 (17.9)
Autologous breast reconstruction	36 (3.6)
Implant breast reconstruction	29 (2.9)
Breast reconstruction, unknown type	17 (1.7)
Unknown	12 (1.2)
Axillary surgery[a]	
Axillary lymph node dissection	257 (25.5)
Sentinel node procedure	569 (56.6)
Other	10 (1.0)
No axillary treatment/unknown	169 (16.8)
Systemic treatment	
Chemotherapy alone	161 (16.0)
Hormonal therapy alone	106 (10.5)
Both chemotherapy and hormonal therapy	464 (46.2)
No adjuvant treatment	241 (24.0)
Unknown	33 (3.3)
Smoking	
Never	455 (45.3)
Current smoker	134 (13.3)
Previous smoker	413 (41.1)
Unknown	3 (0.3)
Diabetes mellitus	
Yes	83 (8.3)
No	922 (91.7)
Body mass index (median (IQR))[b]	27.4 (7.1)
Unknown	228 (25.3)
Type of radiation therapy	
Local	336 (33.4)
Locoregional	264 (26.3)
Unknown	405 (40.3)

Radiotherapy boost[c]	
Yes	372 (39.4)
No	396 (37.0)
Unknown	237 (23.6)
Radiotherapy fractionation[d]	
6-12 fractions	15 (1.5)
15-19 fractions	231 (23.0)
21-24 fractions, with boost	176 (17.5)
20-25 fractions, no boost	122 (12.1)
>26 fractions	88 (8.8)
Unknown	373 (37.1)
Previous radiotherapy breast / chest wall[a]	
Yes	51 (5.1)
No	699 (69.6)
Unknown	255 (25.4)
Months since radiotherapy (median (IQR))	22 (35)

Numbers are shown as *n* (%) unless stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and median(IQR) otherwise.
[a] Total other than 100% due to rounding. [b] Calculated as weight / height^2 [c] An additional radiotherapy boost on the tumor bed or axillary / lymph node boost [d] Dose per fraction was unknown.
Abbreviations: SD standard deviation, IQR interquartile range.

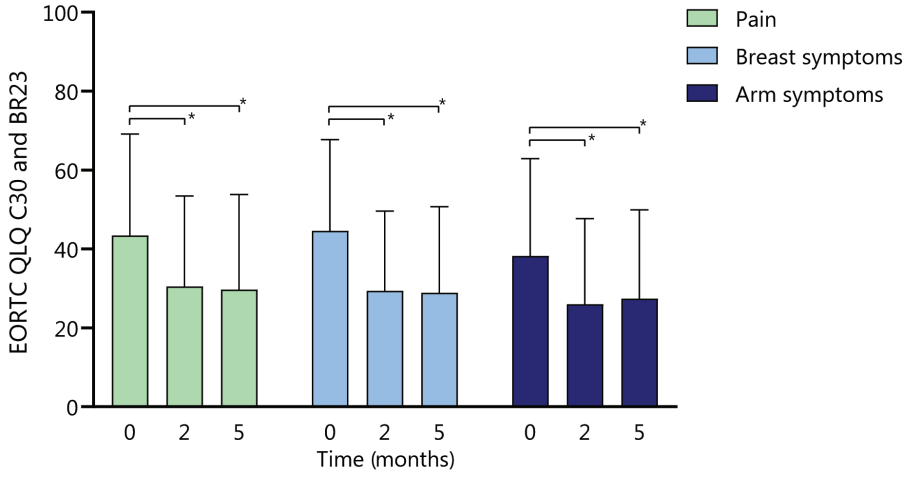
EORTC breast pain scores were available at baseline and at the end of HBOT for 749 patients. In total, 61.5% (*n* = 461/749) of the patients reported breast pain grade 3-4 prior to treatment and 30.0% (*n* = 225/749) reported breast pain grade 3-4 after HBOT. Of the patients with pain grade 3-4 at baseline, 271 patients (58.8%) had grade 1-2 pain at end of treatment and 190 patients still had pain grade 3-4 (i.e., treatment failures) after HBOT (Table 3). Factors associated with treatment success were smoking and time since radiotherapy. Of the patients who smoked during HBOT, 45% (*n* = 29/64) had good response (i.e., no / mild pain after HBOT), 61% (*n* = 121/199) of the never smokers, and 61% of the former smokers (*n* = 120/198) had good response to HBOT. The median time since radiotherapy was 22 months in the group with good response to HBOT and 17.5 months in the group with persistent pain after HBOT.

Table 2. Number of hyperbaric oxygen treatment sessions, reasons for treatment sessions <40 and side effect of hyperbaric oxygen therapy.

Number of HBO sessions	*n* = 1005
HBO sessions (median(range))	40 (20-60)
< 40 sessions (n (%))	240 (23.9)
40 sessions (n (%))	735 (73.1)
40 sessions (n (%))	30 (3.0)
Reasons treatment sessions < 40	*n* (%)
Sufficient results	31 (13)
No/insufficient results	32 (13)
Complications HBOT	17 (7)
Private circumstances	53 (22)
Medical problems not related to HBOT	29 (12)
Unclear	78 (33)
Total	240 (100)
Side effects of HBOT	
Number of patients with side effects (*n* (%))	697 (69.4)
Number of side effects	882
Mild (transient) side effects	***n* (%)**
Barotrauma grade 0-2[a]	179 (17.8)
Hypoglycemia	2 (0.2)
Myopia	576 (57.3)
Fatigue (newly developed)	52 (5.2)
Complication, unclear	41 (4.1)
Moderate / severe side effects	***n* (%)**
Cataract[b]	1 (0.1)
Barotrauma grade 3-4[a]	26 (2.6)
Barotrauma sinus squeeze	1 (0.1)
Oxygen toxicity	4 (0.4)

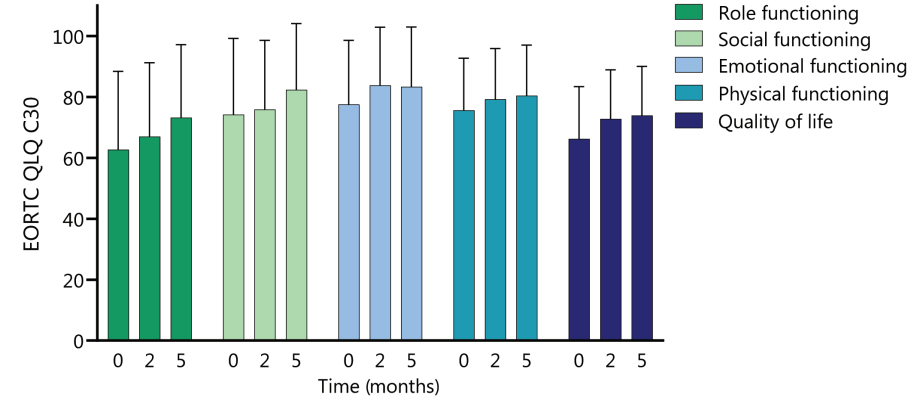
Abbreviations: HBOT hyperbaric oxygen therapy
No cases: chronic oxygen toxicity, cardiac decompensation/heart failure, decompression disease, hypoxia, deceased, pneumothorax. Fatigue was calculated as number of patients with newly developed fatigue during HBOT (i.e., fatigue scores higher than 40 (18))
[a] In accordance with the Macfie classification; [b] Cataract may be therapy induced or pre-existent.

Figure 2. The effect of hyperbaric oxygen therapy on pain, breast symptoms and arm symptoms. A higher score indicates more symptoms.



*Significant difference ($p < 0.05$) tested with Wilcoxon rank test
Time: 0 = baseline (i.e., prior to HBOT), 2 = end HBOT, 5 = 3 months after HBOT

Figure 3. The effect of hyperbaric oxygen therapy on quality of life scores and role, emotional, social and physical functioning using the EORTC QLQ C30 questionnaire. A higher score indicates a better quality of life.



Time: 0 = baseline (i.e., prior to HBOT), 2 = end HBOT, 5 = three months after HBOT

Table 3. Characteristics of patients with and without persistent breast or chest wall pain after hyperbaric oxygen therapy.

	Pain response *n* = 271	**No pain response** *n* = 190
Age (mean (SD))	57.9 (9.7)	57.4 (8.9)
Type of surgery		
Breast conserving surgery	206 (57)	153 (43)
Mastectomy without breast reconstruction	49 (66)	25 (34)
Mastectomy followed by breast reconstruction[a]	13 (57)	10 (44)
Unknown	3 (60)	2 (40)
Systemic treatment		
Chemotherapy alone	40 (56)	31 (44)
Hormonal therapy alone	38 (62)	23 (38)
Both chemotherapy and hormonal therapy	115 (60)	76 (40)
No (neo)adjuvant treatment	68 (54)	58 (46)
Smoking		
Never	121 (61)	77 (39)
Current smoker	29 (45)	35 (54)
Previous smoker	120 (61)	78 (39)
Unknown	1 (100)	0 (0)
Diabetes mellitus		
Yes	18 (55)	15 (46)
No	253 (59)	175 (41)
Body mass index (median (IQR))[b]	27.9 (7.1)	26.6 (7.2)
Radiotherapy boost		
Yes	98 (57)	75 (43)
No	111 (63)	64 (37)
Unknown	62 (55)	51 (45)
Months since radiotherapy (median (IQR))	22 (34)	17.5 (30)

Numbers are shown as *n* (%) unless stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and median (IQR) otherwise.
Patients with breast pain grade 3-4 (EORTC QLQ 50) at baseline were selected. Patients without breast pain was defined as breast pain grade 1-2 at end of HBOT. Patients with breast pain was defined as patients with grade 3-4 breast pain at the end of HBOT.
[a] Total other than 100% due to rounding. [b] Calculated as weight / height^2
Abbreviations: SD standard deviation, IQR interquartile range.

Discussion

In this large cohort study of breast cancer patients with late radiation toxicity, a reduction of pain, breast and arm symptoms and an improvement in patient reported outcomes (i.e., quality of life and social, role, emotional, and physical functioning) following treatment with HBOT was seen. The majority of the patients in this study experienced some side effects of HBOT. The most common side effects were (transient) myopia and mild barotrauma. Myopia and mild barotrauma are transient side effects and dissapear mostly in the first three months after HBOT. This study confirmed that HBOT is a safe treatment, as severe side effects were seen in 3.6% of all patients and mostly concerned barotrauma's.

Two previous studies evaluated the effect of HBOT for breast cancer patients with late radiation toxicity. In the prospective cohort study by Carl et al., outcomes of 32 breast cancer patients treated with HBOT were compared with 12 control patients who refused HBOT (12). Late radiation toxicity was evaluated using the LENT-SOMA scores on a 4-point Likert scale. Similar to our study, a significant reduction in pain was seen after HBOT. Eleven months after treatment, median pain scores for the HBOT group decreased from 3 (range 1-4) prior to HBOT to 0 (range 0-2). The median pain score in the observational group remained stable at grade 3 over time. Like us, Carl et al. reported a significant reduction of edema after HBOT. This reduction of edema was not seen in the control group. In contrast to our study, no effect on physician-reported fibrosis was reported by Carl. et al. In the study by Carl et al. the median fibrosis score was already 0 in both groups prior to the study; so, no effect of HBOT on fibrosis could be seen.

In the prospective study by Teguh et al., 57 patients with late radiation toxicity received on average 47 HBO sessions on 2.4 ATA (11). Late radiation toxicity was evaluated by means of the EORTC QLQ C30 and BR23. Moderate / severe breast pain was seen in 66.7% of the patients prior to HBOT, which is similar to 61.5% in our study. At the end of HBOT, 14.5% of the patients reported moderate / severe pain. This proportion was 30.0% in our study. In the study from Teguh et al. 51% of the patients received chemotherapy and 6/57 (11%) of the patients had no surgery in contrast to, respectively, 72% and at most 1.2% in our population. Consequently, there might be more fibrosis in our population and treatment with HBOT could therefore have been less effective. Proportions of moderate / severe

swelling of breast- and arm and problems with moving the arm prior to HBOT and after HBOT in the study of Teguh et al. were comparable to our study.

In our study, pain response was defined as a decrease in pain from grade 3-4 to 1-2 after HBOT. The proportion of patients that still experienced pain after HBOT was higher in the group of patients that actively smoked in comparison to patients who were never or former smokers. HBOT induces neo-vascularization and smoking might damage these newly developed vessels (6). Consequently, patients that actively smoke during treatment might have less effect of the treatment and experience persisting breast pain after HBOT. In addition, the interval between radiotherapy and HBOT was slightly larger (i.e., difference of 5 months) for patients with breast pain response than for patients with persistent pain after HBOT. A possible explanation is that when radiotherapy is longer ago, it could be more straightforward to differentiate late radiation toxicity from side effects of other breast cancer treatments. As HBOT is specifically targeted for late radiation toxicity, better selection of patients eligible for HBOT may lead to better treatment results. Also, patients who suffered longer from breast pain may report a larger difference in breast pain as they are more relieved than patients who suffered breast pain shortly.

Our study suffers from several limitations: first, clinical outcome data were collected retrospectively, which may have introduced some room for information bias. For example, there may be an underestimation of side effects of HBOT as, theoretically, not all physicians consequently reported side effects in the patient records. To ensure data quality, independent monitoring of extracted data was performed. While monitoring, no discrepancies in extracted data and source date were seen. Second, despite a very high response rate at baseline and at the end of treatment, the response rate at 3 months after the end of treatment was suboptimal (58%). This is partly due to the fact that not all patients were contacted at 3 months after HBOT. Also, the response rate depends on the response of the patients to the EORTC QLQ. In case the response was selective, this may have over- or underestimated the impact of HBOT on PROs. Some patient characteristics differed between non-responders and responders, as non-responders were on average older and received radiotherapy longer ago. Also, the reason for non-response is unknown. Therefore, the effect of HBOT could have been different for non-responders than reponders. Third, no long-term follow-up was available for

this study and no control group was included. Potentially, symptoms and quality of life could also have improved over time (i.e., regressed to the mean) without treatment of HBOT (20,21). As there was no control group, no distinction could be made between regression to the mean and the effect of HBOT. Therefore, the study results need to be confirmed in a randomized controlled trial in order to compare HBOT to a control group. For that reason, we are currently conducting a randomized controlled trial following the Trials within Cohorts design in our institute (NCT04193722) (22). In this trial, the effect of HBOT on late radiation toxicity is compared to usual care in breast cancer patients.

In conclusion, this large study of consecutive breast cancer patients with late radiation toxicity shows a beneficial effect of HBOT on patient-reported symptoms and quality of life and functioning until at least three months after HBOT. Also, it confirms that hyperbaric oxygen therapy is safe, as severe side effects were limited. The most common side effects were (reversible) myopia and mild barotrauma . Due to the non-comparative design of the study, these results need to be confirmed in a randomized controlled trial.

Aknowledgements

The authors thank Denise Joseph for her contribution to the data collection.

Supplementary table 1. Characteristics of responders vs. non-responders to questionnaires.

	Questionnaire responders *n* = 526	**Non-responders to questionnaires** *n* = 479
Age (mean (SD))	59.0 (9.6)	56.8 (9.7)
Type of surgery[a]		
Breast conserving surgery	379 (72)	352 (74)
Mastectomy without breast reconstruction	104 (20)	76 (16)
Mastectomy followed by breast reconstruction	40 (8)	42 (9)
Unknown	3 (1)	9 (2)
Axillary surgery[a]		
Axillary lymph node dissection	141 (27)	116 (24)
Sentinel node procedure	293 (56)	276 (58)
Other	5 (1)	5 (1)
No/unknown	87 (17)	82 (17)
Systemic treatment[a]		
Chemotherapy alone	83 (16)	78 (16)
Hormonal therapy alone	64 (12)	42 (9)
Both chemotherapy and hormonal therapy	247 (47)	217 (45)
No (neo)adjuvant treatment	115 (22)	126 (26)
Unknown	17 (3)	16 (3)
Smoking		
Never	239 (45)	216 (45)
Current smoker	65 (12)	69 (14)
Previous smoker	221 (42)	192 (40)
Unknown	1 (0.2)	2 (0.4)
Diabetes mellitus		
Yes	41 (8)	42 (9)
No	485 (92)	437 (91)
Body mass index (median (IQR))[b]	28.0 (6.8)	28.3 (7.8)
Radiotherapy fractionation[a]		
6-12 fractions	8 (2)	7 (2)
15-19 fractions	120 (23)	111 (23)
21-24 fractions, including boost	91 (17)	85 (18)
20-25 fractions, no boost	63 (12)	59 (12)
>26 fractions	47 (9)	41 (9)
Unknown	197 (38)	176 (37)
Months since radiotherapy (median (IQR))	48.0 (41)	36.9 (31)

Numbers are shown as *n* (%) unless stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and median (IQR) otherwise. Responders was defined as patients who filled in all questionnaires (i.e., baseline, at end of treatment and at 3 months follow-up after HBOT).
[a] Total percentage other than 100% due to rounding. [b] Calculated as weight / height^2
Abbreviations: IQR interquartile range, SD standard deviation

Supplementary table 2. The effect of hyperbaric oxygen therapy on pain, breast symptoms and arm symptoms using all available cases vs. complete cases

		Pain			**Breast symptoms**			**Arm symptoms**		
	Time	0	2	5	0	2	5	0	2	5
All available cases	Mean	43.4	30.5	29.7	44.6	29.4	28.9	38.2	26.0	27.4
	n	951	842	567	921	809	566	919	811	565
	p-value	Ref.	<0.001	<0.001	Ref.	<0.001	<0.001	Ref.	<0.001	<0.001
Complete case analysis	Mean	42.4	30.6	29.2	44.5	30.4	28.8	37.8	26.7	27.4
	n	352	352	352	352	352	352	352	352	352
	p-value	Ref.	<0.001	<0.001	Ref.	<0.001	<0.001	Ref.	<0.001	<0.001

Time: 0 = baseline (i.e. prior to HBOT), 2 = end HBOT, 5 = three months after HBOT
Ref. = reference category
A complete case was defined as a patient who filled in the EORTC questionnaires on all time points. Differences between T0 and resp. T1 and T2 were calculated using a Wilcoxon rank test. Pain, breast symptoms, and arm symptoms were calculated by means of the EORTC QLQ C30 and BR23. Scores ranged from 0 to 100. A higher score indicated more symptoms.

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7

Assessing the effect of hyperbaric oxygen therapy in breast cancer patients with late radiation toxicity (HONEY trial): a trial protocol using a trial within a cohort design

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Trials (2020)

Abstract

Background: Breast cancer treatment with radiotherapy can induce late radiation toxicity, characterized by pain, fibrosis, edema, impaired arm mobility and poor cosmetic outcome. Hyperbaric oxygen therapy (HBOT) has been proposed as treatment for late radiation toxicity; however, high-level evidence of effectiveness is lacking. As HBOT is standard treatment and reimbursed by insurers, performing classic randomized controlled trials is difficult. The "Hyperbaric OxygeN therapy on brEast cancer patients with late radiation toxicity" (HONEY) trial aims to evaluate the effectiveness of HBOT on late radiation toxicity in breast cancer patients using the trial within cohorts (TwiCs) design.

Methods: The HONEY trial will be conducted within the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA). Within UMBRELLA, breast cancer patients referred for radiotherapy to the University Medical Centre Utrecht are eligible for inclusion. Patients consent to collection of clinical data and patient-reported outcomes and provide broad consent for randomization into future intervention studies. Patients who meet the HONEY in- and exclusion criteria (participation $\geq$ 12 months in UMBRELLA, moderate / severe breast or chest wall pain, completed primary breast cancer treatment except hormonal treatment, no prior treatment with HBOT, no contraindications for HBOT, no clinical signs of metastatic or recurrent disease) will be randomized to HBOT or control group on a 2:1 ratio (n = 120). Patients in the control group will not be informed about participation in the trial. Patients in the intervention arm will undergo 30-40 HBOT treatment sessions in a high pressure chamber (2.4 atmospheres absolute) where they inhale 100% oxygen through a mask. Cohort outcome measures (i.e., physical outcomes, quality of life, fatigue, and cosmetic satisfaction) of the HBOT group will be compared to the control group at 3 months follow-up.

Discussion: This pragmatic trial within the UMBELLA cohort was designed to evaluate the effectiveness of HBOT on late radiation toxicity in breast cancer patients using the TwiCs design. Use of the TwiCs design is expected to address issues encountered in classic randomized controlled trials, such as contamination (i.e., HBOT in the control group) and disappointment bias, and generate information about acceptability of HBOT.

Trial registration: Clinicaltrials.gov. NCT04193722. Registered 10 December 2019.

Key words: Breast cancer, Radiotherapy, Hyperbaric oxygen therapy, Late toxicity, Trials within cohorts, Patient-reported outcomes.

Background

With increasing incidence and survival of breast cancer, and the therefore growing number of breast cancer survivors, long-term outcomes and side effects after breast cancer and breast cancer treatment have become increasingly important (1). In most parts of the world, radiotherapy is part of the multimodality treatment of breast cancer in the majority of patients (1). Radiotherapy reduces the risk of local recurrence and improves disease-free survival (2,3). However, it may also induce late radiation toxicity, including breast or chest wall pain, fibrosis, edema, impaired arm mobility, and decreased cosmetic outcome at least 12 months after radiation treatment.

One of the proposed treatment options for late radiation toxicity in breast cancer patients can be hyperbaric oxygen therapy (HBOT). HBOT induces neovascularization and stimulates collagen formation by fibroblasts (4). Although HBOT is currently used in the treatment of late radiation toxicity in the breast and reimbursed by insurers, evidence of clinical effectiveness is limited (5,6). Also, HBOT has several side effects, such as (transient) myopia (12.8%), fatigue (14.0%), barotrauma (i.e., problems with clearing the ears due to the high pressure) (15.1%), or oxygen toxicity (0.003-1.7%) (5,7,8). Oxygen toxicity is characterized by seizures, which will resolve after removal from the hyperbaric tank. Patients suffer from no additional consequences due to the oxygen toxicity and might even finish the other HBOT sessions (8). Several small, non-randomized studies with limited follow-up have suggested a beneficial effect of HBOT in breast cancer patients, especially in terms of pain and arm mobility (5,6).

Conducting randomized controlled trials (RCTs) with HBOT is challenging. First, patients with severe complaints may, when asked to participate in an RCT, refrain from participation because they do not want to be randomized to the control arm (9). Also, participants might drop out after being randomized to the control arm, and obtain HBOT at their own initiative. An alternative trial design to overcome these issues is the trials within cohorts (TwiCs) design (10). In TwiCs, the trial is nested in a prospective cohort study with regular outcome measurements. Eligible patients meeting the trial-specific inclusion criteria will be randomized to an intervention group or control group. Patients allocated to the intervention group will then be offered the intervention. The control group will not be informed about the trial. By using the cohort outcome measurements, outcomes in the intervention group are compared to outcomes in the control group.

In this study, we use the TwiCs design to investigate the effectiveness of hyperbaric oxygen therapy in comparison to usual care in breast cancer patients with late radiation toxicity.

Methods

Study design

This study will be performed within the UMBRELLA cohort (11). In the prospective UMBRELLA cohort all breast cancer patients referred for radiotherapy to the University Medical Center Utrecht are eligible for inclusion. Currently, over 3300 patients are included and inclusion is ongoing. Upon inclusion patients consent for (re)use of their clinical data, collection of patient reported outcomes (PROMs) and they provide broad consent for randomization into future intervention studies (12).

The HONEY study follows the TWICs design (10). Within the UMBRELLA cohort, eligible patients (i.e., patients with late radiation toxicity), who consented for future randomization, will be identified as a sub-cohort for the HONEY trial. Patients from this sub-cohort will be randomized in a 2:1 ratio. Afterwards, patients allocated to the intervention arm will be offered HBOT, which they can accept or refuse (Figure 1). Patients who refuse HBOT will receive usual care, but remain in the intervention arm. Patients who were allocated to the control arm will receive usual care and will not be informed about the trial. Their outcomes will collected within the standard follow-up of the UMBRELLA cohort.

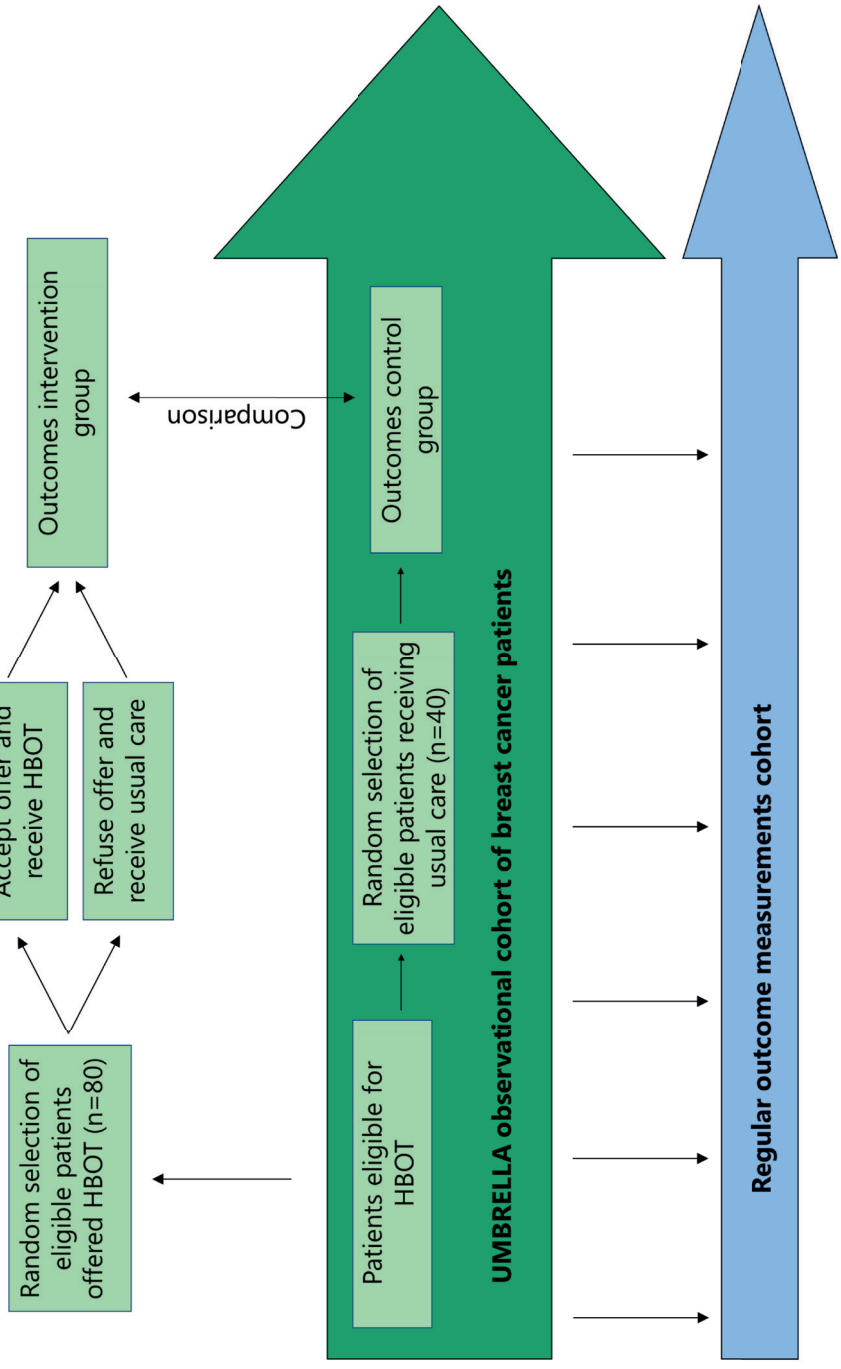

Figure 1. Design of the UMBRELLA HONEY trial; a trial within cohorts design (TWICs design); figure adapted from Relton et al. (10).

Patients with late radiation toxicity will be eligible for participation in the HONEY trial. In order to identify patients with late radiation toxicity, a self-developed late radiation toxicity questionnaire will be send out to UMBRELLA participants who are > 12 months after the last radiotherapy fraction. The late radiation toxicity questionnaire consists of questions from different validated questionnaires. Breast and chest wall pain, social functioning, and other breast symptoms will be assessed with questions from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30), the breast specific questionnaire EORTC QLQ BR23, and Common Terminology Criteria for Adverse Events (13,14). In addition, specific questions were added by the researchers to asses possible late radiation toxicity in further detail and to evaluate eligibility criteria for the HONEY trial.

Eligibility criteria include self-reported breast pain or chest wall pain score in the late radiation toxicity questionnaire of 3 or 4 (on a scale of 1 to 4) and completed primary treatment for breast cancer (except endocrine treatment). Patients are ineligible when they were previously treated with HBOT, have contraindications for HBOT (e.g., (severe) COPD / asthma, pacemaker, morbid obesity, epilepsy in medical history, severe heart failure), have current metastatic disease or recurrent breast cancer or when they are poor responders to UMBRELLA questionnaires (i.e., return of ≤ 2 questionnaires).

Randomization and informed consent

In addition to the primary endpoints, other effects for the patients receiving hyperbaric oxygen therapy (i.e., tissue oxygenation, side effects of HBOT, physician reported outcomes) will be important to evaluate. As a large effect was assumed, the sample size needed to demonstrate a significant effect was rather small. Therefore, in order to be able to answer secondary research questions, a 2:1 ratio for HBOT vs. control group randomization was applied to increase the size of the intervention arm.

A computer-generated randomization list with varying block sizes (n = 3-6) will be generated by an independent data manager prior to the first inclusion. Randomization will be stratified for time since inclusion in the UMBRELLA cohort (i.e., ≤ 2.5 years or > 2.5 years after start radiotherapy). The randomization list is linked to a specially designed inclusion database in Microsoft Access. The

investigator has no access to the randomization list. After enrolment in the inclusion database, Microsoft Access will allocate patients to their respective treatment.

Figure 2. Schedule of enrollment, interventions, and assessments in the HONEY study.

	Recruitment and randomization UMBRELLA cohort		**Measurements HONEY study**			
TIMEPOINT	First consultation with radiation oncologist	Baseline HONEY[a]	Baseline HONEY[a]	Start HBOT	End HBOT	3 months after HBOT
ENROLLMENT						
Informed consent UMBRELLA cohort	X					
Eligibility screening HONEY		X				
Randomization		X				
Informed consent HONEY study (intervention group)		X				
INTERVENTIONS						
Hyperbaric oxygen therapy						
Control (usual care)						
ASSESSMENTS						
Regular questionnaires UMBRELLA cohort	X			X		X
Additional measurements intervention group:						
Physical examination			X	X	X	X
Medical photograph			X			X
TCOM				X	X	

[a] At least 12 months after UMBRELLA inclusion.
Abbreviations; HBOT – hyperbaric oxygen therapy; TCOM – transcutaneous oxygen measurement

In accordance with the TWICs design, patients randomized to the HBOT arm will be contacted by the investigator and offered to undergo HBO treatment. If they agree, they sign a second informed consent form in addition to the previously signed informed consent form of the cohort. Also, patients have the option to

consent for the use of their clinical data for other studies on the same subject. In case patients drop out after providing informed consent, patients are asked for permission for the use of their clinical data in the trial. This trial does not involve collecting biological specimens for storage. The informed consent form is available from the corresponding author upon request. Patients who refuse the offer to undergo HBOT will receive treatment as usual, i.e., standard follow-up. Standard follow-up may entail physiotherapy, edema therapy and / or analgesics, depending on the patient's needs. Patients who are allocated to the control arm will not be informed about the HONEY trial, and undergo standard follow-up. For logistic reasons and planning of HBOT, patients will be recruited in batches (Figure 2). After confirmation of diagnosis by a radiation oncologist, patients provide informed consent and will be referred for hyperbaric oxygen therapy.

Hyperbaric oxygen therapy group

The combination of high pressure and 100% oxygen inhalation induces neovascularization and regeneration in the irradiated (hypoxic) tissue (4). During HBOT, patients are seated in a hyperbaric chamber in which the pressure will be raised from 1.0 atmospheres absolute (ATA) to 2.4 ATA. Subsequently, 100% oxygen is given through a mask placed over nose and mouth for 20 minutes. One treatment session of HBOT is divided into 4 parts of maximum 20 minutes during which patients inhale 100% oxygen. In between these parts, there are small breaks without a mask, to decrease the risk on oxygen toxicity. After the oxygen sessions the pressure will be decreased to 1.0 ATA.

To make sure patients are eligible for hyperbaric oxygen therapy, patients will be seen by a hyperbaric oxygen therapy physician. If patients are not "fit to dive" (e.g., in case of a respiratory tract infection) in between HBOT sessions or prior to HBOT, the HBO physician might decide to cancel a HBOT session to ensure patients safety. In case of missed HBO sessions, the HBO physician will decide whether effectivity of HBOT is endangered. Depending on judgement of the hyperbaric oxygen physician, the HBOT might be cancelled or prolonged at the end.

HBOT consists of 30-40 hyperbaric oxygen sessions (i.e., one session of 2 hours per day, 5 days / week). There are appointments with the HBO physician scheduled after 15 and after 30 HBO sessions, since the first effects of HBOT on late radiation toxicity will occur after 20-30 HBO sessions. Therefore, the patient and the HBO physician will decide together whether or not an additional 10 sessions will be

valuable after 30 HBO sessions, depending on the effects achieved with HBOT so far. In between hyperbaric oxygen sessions, patients in the intervention group might still require edema therapy, physiotherapy or use analgesics (i.e., usual care). All concomitant care is permitted; the use of these treatments will be monitored.

Control group

The patients randomized to the control group will not be notified about the UMBRELLA HONEY trial and will receive usual care. As usual care entails many different treatment options, including HBOT, patients in the control group will be monitored to evaluate the treatment they undergo for the late radiation toxicity.

Primary and secondary endpoints

The primary endpoint of this study is the difference in proportion of patients with severe / moderate reported breast / chest wall pain between both groups at 3 months follow-up (Figure 2). Upon inclusion, all patients will have moderate / severe pain, as this is an inclusion criterion. Self-reported pain is assessed through the late radiation toxicity questionnaire on a 4-point Likert scale (i.e., none / mild / moderate / severe). Self-reported pain is dichotomized into none / mild pain and moderate / severe pain.

Secondary endpoints include physical functioning, QoL, cosmetic outcome, physician-reported pain and radiation toxicity, tissue oxygenation and side effects of HBOT. Physical functioning will be evaluated using the late radiation toxicity questionnaire, containing questionnaires on breast and arm edema, arm mobility, and breast fibrosis. QoL will be assessed by means of the EORTC QLQ C30 and breast specific questionnaire EORTC QLQ BR23 (13). In the UMBRELLA cohort, QoL is measured upon inclusion (before start radiotherapy), at 3 months, and every 6 months afterwards. Self-reported cosmetic outcome will be assessed using the BREAST-Q questionnaire (15,16). Depending on previous surgery, patients fill out a different module (mastectomy / breast conserving therapy / reconstruction) yearly within the UMBRELLA cohort. Side effects will be monitored using the MacFie classification (17).

Additional measurements intervention group

Patients included in the intervention arm, who accepted to undergo HBOT, will visit the UMC Utrecht prior to the start of HBOT and 3 months after the last

hyperbaric oxygen session (Figure 2). The first visit is a combined visit to obtain informed consent, perform physical examination by a radiation oncologist to confirm diagnosis, and obtain a standardized digital photo for cosmetic outcome.

Physical examination includes breast and / or chest wall examination to assess the extent of baseline toxicity edema and fibrosis according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (14). The Patient and Observer Scar Assessment Scale (POSAS) will be used as a scar rating scale (18). The extent of impaired arm mobility will also be assessed. Upon inclusion auscultation of the heart and lungs and an ear exam will be performed to assess eligibility for HBOT.

Three months after the last hyperbaric oxygen session, patients will visit the UMC Utrecht again for physical examination and a medical photo.

Transcutaneous oxygen measurement

Shortly prior to the HBOT, transcutaneous oxygen measurement (TCOM) will be performed and repeated 3 months after the last HBOT session (Figure 2). TCOM is a local and non-invasive measurement (19). With 2-4 sensors on the skin, the diffused oxygen in the skin is measured. The temperature in the sensor is slightly increased during measurement, inducing vasodilatation. Oxygenation of tissue with late radiation toxicity will be compared before and after HBOT, and to the contralateral breast without late radiation toxicity.

Medical photograph

A medical photograph will be taken prior to the first HBOT session and 3 months after the last HBOT session. This digital photo will be judged by expert physicians (with different medical backgrounds) to assess cosmetic outcome. These physicians will be blinded for the moment the digital photo was taken (i.e., prior or after HBOT). In addition, the symmetry of the breast (in case of breast conserving surgery or breast reconstruction) will be assessed by the BCCT.core program (20).

Data management and trial monitoring

Every 3 months, the trial proceeding is evaluated by the trial steering group. The trial steering group consists of the principal investigator, study coordinator and supervising staff members of the UMC Utrecht. Daily coordination, recruitment

of subjects, and inclusion of trial subjects are the responsibility of the study coordinator.

In addition, study progress and data management are evaluated by an independent trial monitor. The trial monitor evaluates adherence of the data management plan, protocol adherence and trial progress prior to the start of the trial, after inclusion of 5 patients, and yearly afterwards. At the end of the trial (i.e., after the last patient had the last visit to the UMC Utrecht) a closing visit will be scheduled. The data management plan encompasses detailed information on data collection and storage (Additional file 1). The independent trial monitor will report outcomes of the monitoring to the institutional review board. A Data Monitoring Committee was not considered as HBOT is a low-risk intervention. The trial sponsor played no part in the study design, writing the report, or decision to submit the report for publication. Also, the trial sponsor will not play a part in collection of data, study management, and data analysis.

Aggregated results of the trial will be reported to all UMBRELLA patients after analysis through the annual newsletter. No post-trial care is scheduled, as no long-term harm of HBOT is anticipated. During the trial, the physicians of trial patients will be informed about the participation. Trial results will be published after analysis. Any data required to support the trial protocol as well as trial data can be supplied by the corresponding author upon reasonable request.

Sample size considerations

Since moderate / severe pain is an inclusion criteria, all patients will have moderate or severe pain upon inclusion. We assume that 3 months after the last hyperbaric oxygen session, the proportion of patients treated with HBOT suffering from moderate to severe pain will decrease to 30% (5). Both control patients and patients who refuse HBOT will receive usual care. It is not expected that the offer of HBOT will influence the outcome at follow-up. Consequently, we assume that of the patients receiving usual care, at least 80% will be reporting moderate / severe pain at the same time point.

It is expected that 50% of the women in the HBOT arm, who will be offered HBOT, will accept and undergo the treatment. As such, in the intervention arm, the overall proportion of women reporting moderate to severe pain will be 55% (0.5 x 30% + 0.5 x 80%) and 80% in the control group. In line with the TWICs design, the control

patients are not informed about the HBO treatment. Consequently, there will be no refusal in the control arm.

The purpose of this study is to evaluate if HBOT is either similar or better than usual care. Therefore, a directional (i.e., one-sided) test will be used. To demonstrate a significant difference of 55% vs. 80% with a power of 80%, a one-sided alpha of 0.05, and an inclusion ratio of HBOT vs. control group of 2:1, we need 72 patients in the HBOT arm and 36 patients in the control group. However, drop-out might be expected. These are not patients who refuse participation, but drop-out for other reasons, such as patients who no longer wish to participate in the UMBRELLA cohort or patients who accept the offer of HBOT, but drop-out afterwards. In order to adjust for 10% drop-out, a total of 120 (80:40) patients will be enrolled in the UMBRELLA HONEY trial. Enrollment is expected to take 20 months.

Data analysis

Outcomes of eligible patients who were randomly offered HBOT will be compared with eligible patients who were randomly selected from the control group. In case of non- or incomplete compliance with the intervention (i.e., patients not finishing all 30-40 HBO sessions), a worst-case analysis will be performed: dropped-out patients will be classified as non-responders. As part of the TwiCs design, non-compliance is only expected in the intervention group. In addition, patients in the control group may also undergo HBOT outside the trial setting. To account for the non-compliance in the intervention group and possible contamination in the control group, a Complier Average Causal Effect (CACE) analysis will be used in addition to the intention to treat analysis (21,22). In a CACE analysis, the group who accepted the HBOT will be compared to the control group who would have accepted the intervention if they had received the offer.

The primary outcome will be presented in absolute numbers and proportions. The primary outcome is defined as difference in proportion of patients with moderate /severe pain at 3 months follow-up per allocated treatment arm (i.e., intervention or control group). As pain is measured on a 4-point Likert scale, it will be dichotomized into no / mild pain and moderate / severe pain. Pain response is defined as decrease in pain from self-reported moderate / severe pain to no / mild pain. Differences in pain response will be compared by χ^2 test. As secondary analysis, an unadjusted logistic regression analyses will be performed. In addition,

as sensitivity analysis, the logistic regression analysis will be adjusted for age, time since radiotherapy, radiotherapy dose, and smoking. There will potentially be missing data. Assuming that missing values are missing at random, multiple imputation by chained equations for the primary analysis will be used to replace missing values, using 20 imputed datasets (23–26). In addition, complete case analysis will be performed as sensitivity analysis. Toxicity will be presented as the overall incidence of grade 2–4 toxicity. QoL outcomes will be evaluated at 3 time points: baseline in the UMBRELLA cohort, prior to HBOT, and at follow-up. To account for the intra-subject correlation over time, a mixed model for repeated measurements will be used. In the model, a random intercept and random linear time effect and an autoregressive covariance structure of the first order (AR1) (assuming that the correlation systematically decreases with increasing distance between time points) will be included (27). Also, fixed effects for treatment arm and an interaction between time and treatment arm will be included, as well as characteristics with imbalances as previously described. Differences with a p-value < 0.05 will be considered statistically significant.

Given the relatively small sample size of the study, we will not be performing an interim analysis, as it is very unlikely that we will see a highly significant effect of HBOT justifying early stopping of the trial. Also, there is ample clinical evidence that HBOT is safe and associated with a very small risk of mild side effects. Therefore, no side effects are expected that might lead to early termination of the study. Consequently, no interim analysis was planned for this study.

Ethical approval

Ethical approval was obtained for both the UMBRELLA study (including the TWICs infrastructure) and the HONEY trial (protocol version 3, d.d. 23 July 2019) from the institutional review board of the UMC Utrecht. The UMBRELLA study was published under NCT02839863 (11) and the HONEY study under NCT04193722 on ClinicalTrials.gov.

Discussion

The HONEY study aims to assess the effectiveness of hyperbaric oxygen therapy on late radiation toxicity in breast cancer patients. HBOT is by some considered as

a potentially curative treatment for late radiation toxicity in breast cancer patients. In a study by Teguh et al., the effects of 40 sessions with HBOT of 57 patients with late radiation toxicity were assessed. Pain score was assessed by means of the NRS score (5). An improvement of ≥ 1 point immediately after treatment was seen in 81% of the patients. Also, a significant improvement of self-reported arm mobility, swelling of the breast, and arm, skin problems, oversensitivity of the breast, and pain in arm, or shoulders immediately post-HBOT was observed (assessed by EORTC BR23). However, limitations of this study are the absence of a control group and the small sample size.

In a prospective study, Carl et al. compared 32 breast cancer patients treated with HBOT with 12 patients who refused to undergo HBOT. The median number of HBOT sessions was 25 and ranged from 7 to 60 sessions, since treatment was stopped when 3 consecutive sessions did not result in improvement. Late radiation toxicity was assessed by means of the LENT-SOMA score, a score conducted through physical examination (28). In this small, non-randomized study, a significant reduction in pain, edema, and erythema of HBOT patients in comparison to non-treated patients was seen. In conclusion, evidence is limited and a randomized trial is needed.

Currently, HBOT is reimbursed by insurers for symptoms of late toxicity, complicating evaluating its efficacy in a classic RCT. In a classic RCT comparing usual care to HBOT, patients allocated to the control arm may be disappointed and report worse outcomes, leading to disappointment bias. Also, patients might drop out after being randomized to the control group and undergo HBOT at their own initiative. A classic randomized controlled trial by Teguh et al. randomized 19 patients with oropharyngeal and nasopharyngeal for HBOT or control group (usual care) immediately after radiotherapy (9). Prior to HBOT, self-reported complaints, such as dry mouth, were significantly higher for control patients than HBOT patients, despite randomization. Also, the study was stopped prematurely due to slow accrual, leading to only 19 patients eligible for analysis.

An alternative is the sham-controlled trial, in which patients in the control group undergo 40 sham sessions in a hyperbaric oxygen chamber with only slightly elevated air pressure and inhale normal air instead of 100% oxygen. From an ethical perspective, it may be undesirable to expose patients to a high burden, i.e.,

40 2-hour sessions, unnecessary. Previously in a trial by Clarke et al., 150 patients with radiation proctitis were randomized to HBOT or sham-controlled group (29). To overcome the ethical issue of the burden for the control group, patients were crossed-over after 40 sham sessions. Consequently, it is impossible to obtain long-term follow-up results for the control patients with this design.

The TWICs design aims to overcome problems, such as disappointment bias, slow accrual, and drop-out in the control group, since patients in the control group are unaware of being a control. Upon inclusion in the UMBRELLA cohort, patients consent to future randomization and after the trial, the entire cohort will be informed about the results obtained in the HONEY trial. Also, since the HONEY trial participants are also UMBRELLA participants, follow-up can continue for years after completion of HBOT.

A limitation of the TWICs design is the dependency of data collected within the cohort. In order to assure that control patients remain unaware of their participation in the trial, it is for example not possible to perform additional (invasive) physical measurements on these patients. Also, eligibility for the trial is assessed by means of a self-reported questionnaire on late radiation toxicity and not physical examination, in contrast to current practice. However, literature suggests that patient reported late radiation toxicity do not underestimate late side effects reported by physicians (30).

In summary, the HONEY trial is a pragmatic trial in accordance with the TWICs design. The HONEY trial aims to evaluate the efficacy of HBOT in breast cancer patients with late radiation toxicity.

Additional file 1

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8

Summary

Breast cancer treatment, including radiotherapy, may impair the long-term quality of life, especially in patients that experience toxicity after treatment. In this thesis, the impact of breast cancer treatment on long-term quality of life was evaluated and potential solutions for skin toxicity were assessed. **Chapter 2** evaluated satisfaction with cosmetic outcome after breast cancer treatment. Breast cancer treatment inevitably leads to in changes in the breast that may result in scar tissue or – on the other end of the spectrum – a deformed breast. This study showed that the majority of the patients is satisfied with their cosmetic outcome after breast cancer treatment. Dissatisfaction with cosmetic outcome was associated with poorer quality of life, body image and social and emotional functioning. This emphasizes the importance to counsel patients after breast cancer treatment and evaluate the cosmetic outcome after surgery as well as the impact it may have on quality of life.

Breast cancer treatment may also affect the way women feel about themselves, for example to what extend they feel satisfied with their body or if they feel feminine. In **chapter 3**, the body image after breast cancer treatment was evaluated. During four years of follow-up the proportion of patients that experienced poorer body image was (very) small, which may reassure women who are about to start their breast cancer treatment. A poorer body image after one year follow-up was associated with chemotherapy, a higher body mass index, a poorer baseline body image and poorer baseline emotional functioning. This may help breast cancer physicians to identify patients at risk for a poorer body image and inform these patients prior to their treatment.

Approximately 68% of all breast cancer patients is treated with radiotherapy. Even though treatment techniques have improved over the past decades, radiotherapy may result in late toxicity. **Chapter 4** identified determinants associated with local late radiation toxicity in breast cancer patients. Knowing factors that induce late radiation toxicity, may help to evaluate individual treatment adaptation. Also, early intervention to prevent late radiation toxicity could be investigated for patients at risk for late radiation toxicity. This review showed that increased radiotherapy dose (including radiotherapy boost) or increased radiotherapy volume were associated with more late radiation toxicity. There were no clear clinical or patient-related determinants associated with late radiation toxicity. It is important to develop and evaluate new treatment techniques, such as partial breast irradiation, in order to

decrease late radiation toxicity, as late radiation toxicity may impair quality of life. In **chapter 5** self-reported symptoms of late radiation toxicity were evaluated. The most common symptoms of late radiation toxicity were firmness of the breast and breast or chest wall pain. After a median follow-up of 38 months, 16% of the patients reported late radiation toxicity. Patients with self-reported late radiation toxicity reported lower physical functioning, role functioning (i.e., functioning around friends and family or at work) and social functioning in comparison to patients without late radiation toxicity. Consequently, it is important to reduce the proportion of patients that experience late radiation toxicity by preventing late radiation toxicity (i.e., development of new radiotherapy techniques) as well as to find a treatment to reduce late radiation toxicity.

Evidence about the best treatment for late radiation toxicity in breast cancer patients is lacking. One of the proposed treatments is hyperbaric oxygen therapy. In **chapter 6** symptoms of late radiation toxicity in breast cancer patients treated with hyperbaric oxygen therapy were evaluated. After hyperbaric oxygen therapy, a significant reduction in pain, breast and arm symptoms was seen and quality of life improved. The study showed that hyperbaric oxygen therapy is a safe treatment, as the side effects after treatment were low. However, due to the design of this study, treatment outcomes could not be compared to patients who were not treated with hyperbaric oxygen therapy. **Chapter 7** describes a trial within cohorts protocol that will evaluate the effectiveness of hyperbaric oxygen therapy in breast cancer patients with late radiation toxicity. This trial will be conducted in the longitudinal UMBRELLA breast cancer cohort. In UMBRELLA, patients with late radiation toxicity will be selected and randomized to receive hyperbaric oxygen therapy or usual care. According to the trial within cohorts design, outcomes of the control group will be collected within the cohort and patients will be informed about their participation after the study. The intervention group will be offered hyperbaric oxygen therapy and may accept or refuse the intervention. Effectiveness of hyperbaric oxygen therapy (i.e., reduction in breast or chest-wall pain) will be evaluated at 3 months after hyperbaric oxygen therapy.

9

General discussion

There has been an increasing interest in real world data in recent years (1,2). Real world data is defined as data collected during every day clinical practice, such as electronic health records (2,3). There is an increasing data availability, resulting in the possibility to perform observational studies in very large populations (2,4). Consequently, real world data can be useful to detect rare side effects in treatments that are implemented already in routine care (1). Also, using real world data provides for the possibility to combine various data sources (i.e., electronic health records, wearables) in studies, resulting in a more holistic view on the patient's health status (2). When compared with randomized clinical trials, performing research with real world data is less time consuming and less expensive, as existing data sources can be used (3). Other than strictly regulated randomized controlled clinical trials, real world data provide an insight in the clinical decision-making in routine clinical practice (5,6). On the other hand, real world data may not provide a reliable estimation of a treatment effect, as prescription of a treatment is often associated with other clinical factors, such as a patients' health status (i.e., confounding by indication) (1). Although we can adjust for known confounding factors, there may always be residual confounding through unknown confounding factors. As clinical factors are balanced in a randomized trial (i.e., patients are allocated to a treatment arm by chance), their potential effect on the outcome is independent of the treatment group and consequently eliminates the risk of confounding.

The UMBRELLA study is an example of showing that it is possible to combine the best of both worlds: real world data can be successfully combined with randomized controlled trials. The goal of the UMBRELLA study is to evaluate routine clinical practice of breast cancer patients and to provide an infrastructure in which randomized trials can be performed in routine breast cancer care (7). Patient inclusion for the UMBRELLA study started in 2013 and over 3700 patients have been enrolled since. Prior to breast cancer treatment (i.e., before surgery or before radiotherapy), breast cancer patients are invited to consent to the collection of their clinical data for research. In addition, patients may consent to collection of patient reported outcomes (PROs) by means of validated questionnaires and future randomization. From the patients that consent to participate in the UMBRELLA cohort, clinical outcomes, such as survival, treatment toxicity, and quality of life are collected and used to evaluate (novel) breast cancer treatments. The studies performed in UMBRELLA can be used not only to further improve breast cancer

treatment, but also to optimally inform the patients about their treatment expectations in terms of quality of life, toxicity, and survival after breast cancer. UMBRELLA data are used for observational studies, as described in chapter 2 and 3, to evaluate quality of life after breast cancer and determinants associated with poorer body image and cosmetic outcome. As the UMBRELLA study is an ongoing cohort, cohort data are available to answer new research questions within a short period of time, for example, to evaluate the effect of COVID-19 on quality of life of breast cancer patients (8,9).

Some studies have proposed real world observational studies as an alternative for randomized controlled trials (10,11). However, the latter remains the gold standard for evaluation of new treatments (1,5). Randomization ensures that the only difference between two treatment arms is the given treatment, which therefore leads to a decrease in confounding bias (1,5). On the other hand, randomized controlled trials are expensive and time-consuming (2,5). Due to strict in- and exclusion criteria, a trial population may not be representative for the general population (12,13). This may jeopardize the applicability of the trial results in the general population (14). Also, recruitment of eligible participants is often difficult or unsuccessful (15). To overcome these limitations, Relton et al. introduced the Trials Within Cohorts (TWiCs) design (14). In TWiCs, patients are recruited from an existing (longitudinal) cohort with regular outcomes. Prior to inclusion in the cohort, all patients give consent for future randomization. After selection of eligible patients for the TWiCs, patients are randomized to receive usual care or a new intervention. Only the patients allocated to either receive the new treatment are offered the intervention. Patients in the control group receive usual care and are not informed about the trial. In the UMC Utrecht, several TWiCs have been successfully executed (16–18). They showed that the randomized population was representative for the reference population (19). Also, recruitment was successful and efficient. For example, all patients in the UMBRELLA FIT trial (*n* = 260) were recruited by one researcher within 30 months (17). As seen in chapter 5, the TWiCs design may also overcome limitations when the intervention in a trial, such as hyperbaric oxygen therapy, is already implemented in routine clinical care. In a classic randomized controlled trial, patients might drop-out after randomization into the control group (and receive treatment at their own initiative) or report poorer outcomes when randomized to the control group (disappointment bias). In a TWiCs, patients in the control group are unaware of trial participation and will

not receive the intervention at their own initiative and cannot be disappointed due to their treatment allocation.

Although the UMBRELLA study has been successfully implemented in multiple hospitals in the Netherlands, there are several challenges that need to be addressed in order to improve the sustainability of the cohort. A selection in the study sample, for example by missing data or selective study participation, may bias the results (2). In UMBRELLA, quality of life is evaluated regularly through various validated questionnaires prior to breast cancer treatment and every six months thereafter until ten years after breast cancer treatment. Several actions are taken to maintain high response rates, including: (i) sending reminders to patients who have not completed their questionnaires, (ii) sending out annual newsletters to cohort participants and (iii) inviting participants to the "UMBRELLA day", an annual patient conference where results from UMBRELLA study results are presented. Nevertheless, as seen in chapters 2 and 3, the response rate of PRO questionnaires drops gradually over time from 84% at baseline to 52% after 5 years. In addition, there is a number of patients that terminate their study participation early. This increases the risk of distorted outcomes, as bias may occur when cohort engagement (i.e., selective non-response or selective termination of study participation) is associated with the (patient reported) outcome of interest (20,21).

There may be several reasons for patients not to fill in the questionnaires that potentially lead to selective response. To evaluate the degree of selective response, patient, treatment, and tumor characteristics of responders are compared to non-responders in the observational studies. However, other unknown or unmeasured characteristics may be related to quality of life. Also, selective response cannot be ruled out even if measured patient, treatment, and tumor characteristics of responders and non-responders are comparable. Moreover, if characteristics of non-responders differ from those of responders to the questionnaires, it is impossible to evaluate the potential effect this difference in characteristics would have had on the PROs.

These challenges seen in the UMBRELLA cohort (i.e., selective response and termination of study participation) may also impact the validity of trials within the cohort. First, with decreased cohort engagement, the risk of a selective trial population increases and trial results may not be generalizable to the

general breast cancer population. Also, there may be selective response to the questionnaires in a TWiCs. Patients in the intervention group, who have been offered to undergo an experimental intervention, may be more motivated to respond to the questionnaires than control patients who are unaware of their trial participation (17,18). There may be patients that responded to the cohort questionnaires now, but would not have responded had they been allocated to the control group. This may impair the validity of the study as the results of the intervention group may be not be representative of the intervention but from the offer of the intervention (22).

Challenges related to late radiation toxicity

Defining late radiation toxicity

As described in chapter 5, late radiation toxicity is a common problem in women treated for breast cancer. There are various tools that can be used to assess and grade toxicity after breast cancer treatment. These include the Common Terminology Criteria for Adverse Events (CTCAE) (23), Radiation Therapy Oncology Group criteria (RTOG) (24) and Late Effects Normal Tissues-Subjective Objective Management Analytic criteria (LENT-SOMA) (25). However, these three tools use a different definition for late radiation toxicity and a different description of the symptoms related to late radiation toxicity. For example, LENT-SOMA defines grade 1 arm edema as an increase of 2-4 cm in arm circumference, while in CTCAE grade 1 arm edema is defined as a difference of 5-10% in comparison to the other arm. RTOG has no separate grading system for arm edema. Consequently, it is difficult to compare the outcomes of studies using different tools, as is seen in chapter 4, where determinants associated with late radiation toxicity were assessed in a systematic review. Therefore, in order to be able to compare different studies on late radiation toxicity, it is important to establish one clear definition for late radiation toxicity.

Hyperbaric oxygen therapy

Hyperbaric oxygen is a therapy in which patients breathe in 100% oxygen in a high-pressure chamber, which may induce neo-vascularisation (26). As seen in chapter 5, hyperbaric oxygen therapy may decrease breast and arm symptoms for breast cancer patients with late radiation toxicity. Although the hyperbaric oxygen therapy sessions are non-invasive, the treatment is intensive and time-consuming.

Therefore, it is important to accurately select patients that may optimally benefit of this treatment. To this day, high-level (randomized) evidence of the effectiveness of hyperbaric oxygen therapy, the optimal timing of starting hyperbaric oxygen therapy after radiotherapy in breast cancer patients and which patients benefit from hyperbaric oxygen therapy is lacking. Predicting which patients may develop late radiation toxicity is challenging as late radiation toxicity may develop years after treatment has been received (27). Also, the optimal number of hyperbaric oxygen sessions remains unclear, as the number of treatment sessions varied between 20-40 in different studies (28,29). Because of the burden of the treatment, patients may be more reluctant to start hyperbaric oxygen therapy in comparison to, for example, a less intensive treatment such as edema therapy, which may take place once a week. The HONEY trial first needs to confirm treatment effectivity of hyperbaric oxygen therapy for late radiation toxicity in breast cancer patients. A next step could be to identify which patients may benefit most from hyperbaric oxygen therapy.

Conclusion and future perspectives

Real world data may provide a better insight in outcomes in the general breast cancer population (2). The UMBRELLA study successfully uses real world data for research by collecting long-term outcomes of all breast cancer patients in multiple hospitals in the Netherlands. The cohort participation rates are high (88%), meaning that almost all patients who are invited to participate in the UMBRELLA study are included in the cohort (30). As patients consent to randomization within the cohort at baseline, randomized trials using a TWiCs design can be performed within the cohort. The first TWiC within the UMBRELLA study has been performed successfully (17).

It is important to maintain high participation rates (resulting in a representative study sample) for the UMBRELLA study in the future. Potentially, high response rates in the UMBRELLA study were achieved as patients are included at the innovation clinic. Currently, outcomes of the UMBRELLA study are only used for research and not to monitor patients in clinical practice. Some physicians find it helpful to use PROs to identify areas of concern for their patients (31). For that reason, a tool to visualize the PROs in the electronic health records of the UMBRELLA patients is currently being integrated in the study in the future. That way, outcomes of PROs (e.g., quality of life, cognitive functioning, anxiety and depression) are visible for

both patients and physicians and could be used for shared decision making as well as to monitor the patient during and after breast cancer treatment.

A proposed alternative to monitor the quality of life of all patients, is to implement PROs in routine clinical care (32,33). Then, results of these routinely collected data could be used for research. Also, PROs collected in routine clinical care could be used to identify areas of concern for the patients, providing the opportunity to, for instance, start psychological support quickly (31). In theory, collecting PROs as part of standard care will not only emphasize the importance of quality of life after breast cancer for both professionals and the patients, but also stimulate shared decision making based on preferences of the patient. Ideally, the collected PROs can both be used for research in order to improve breast cancer treatment, as well as to monitor patients during and after treatment.

For that reason, PROs were implemented in routine breast cancer care at the Erasmus Medical Center in the Netherlands in 2015 (34). PROs were collected at baseline, after 3 months, after 6 months, and annually thereafter. The questionnaires were sent automatically and the results were filed within the electronic health records of the patient. However, the response rates dropped from 84% at baseline to 65% at 3 months and 55% at 12 months after inclusion. In a systematic review by Van Egdom et al., similar decreasing response rates were seen (varying from a response rate of 13% after 90 days to a maximum response rate of 64% in 1 year in different studies) , when PROs were collected within routine clinical care (31). In UMBRELLA, response rates at 3 months and 12 months are substantially higher, respectively 73% and 69% (Chapter 3). With lower response rates, implementing PROs in routine care may result in more selective response to the PROs in comparison to the UMBRELLA study. This may impair the usability for research of these routine collected PROs.

To date, evidence that collecting PROs in routine clinical care would actually improve health outcomes is lacking (35). Also, the study by Van Egdom et al. showed that the results of PROs collected in routine clinical care were used in only 25% of the patients during outpatient clinical visit and 50% of the patients felt that filling in PROs contributed positively to their breast cancer treatment (34). The UMBRELLA study could be used to evaluate to what extend PROs in routine clinical care improves the outcomes after breast cancer and to what extend PROs improve the satisfaction with breast cancer care for patients and physicians.

Integrating evaluation of quality of life in standard clinical care may not help to overcome challenges in observational cohort studies, such as decreasing response rates and early termination of study participation. For that reason, it is important to evaluate possibilities to increase cohort adherence, for example by reducing the time needed to fill in the questionnaires (e.g., reducing the number of questionnaires or by using computerized adaptive testing) (36,37). With improved cohort adherence, the UMBRELLA study would be the perfect example of the success of real world evidence.

Over the past eight years, the UMBRELLA study provided insight in the quality of life of breast cancer patients during and after breast cancer treatment. Also, with multiple TWiCs implemented in the study, randomized trials can be performed. That way, we keep learning from each patient and continue to improve breast cancer care.

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10

Summary in Dutch

Borstkanker is de meest voorkomende kankersoort onder vrouwen. In Nederland worden jaarlijks ongeveer 17.000 patiënten met borstkanker gediagnosticeerd, meestal bij patiënten tussen de 45-75 jaar. Borstkanker wordt behandeld met (een combinatie van) chirurgie, chemotherapie, hormoontherapie, HER2-gerichte therapie en bestraling (radiotherapie). Door nieuwe behandeltechnieken en vroege opsporing van borstkanker, bijvoorbeeld in het bevolkingsonderzoek, is de 10-jaars overleving van borstkanker verbeterd tot 88%. Mede daardoor neemt het aantal patiënten dat leeft met de gevolgen van borstkanker en borstkankerbehandeling toe.

Het doel van dit proefschrift is om de kwaliteit van leven na borstkankerbehandeling te evalueren en te onderzoeken welke patiënten een verminderde kwaliteit van leven hebben na borstkanker. In het eerste deel van dit proefschrift wordt onderzocht welke eigenschappen (determinanten) samenhangen met een slechtere kwaliteit van leven na borstkankerbehandelingen. Het tweede deel van dit proefschrift richt zich op late bestralingsschade, dus lange termijn toxiciteit van de radiotherapie behandeling. Late bestralingsschade kenmerkt zich door pijn in de borst, verminderde bewegelijkheid van de armen, stugheid (fibrose) van de borst, minder fraai uiterlijk van de borst en oedeem (vocht) in de borst of armen.

Het grootste deel van de onderzoeken in dit proefschrift zijn uitgevoerd binnen de “UMBRELLA” studie. In verschillende ziekenhuizen in Nederland worden patiënten voorafgaand aan hun borstkankerbehandeling, bijvoorbeeld voor de eerste bestraling, gevraagd of ze aan de UMBRELLA studie willen deelnemen. Bij deelname kunnen patiënten kiezen waar ze toestemming voor geven: verzamelen en gebruik van medische gegevens, invullen van vragenlijsten en toestemming om randomisatie voor toekomstige studies. Dit laatste houdt in dat als er een nieuwe behandeling onderzocht gaat worden, een groep deelnemers zal loten (gerandomiseerd wordt) voor een nieuwe behandeling en een deel zal loten voor dezelfde behandeling die anders ook gegeven zou worden. Toestemming voor randomisatie betekent dus toestemming voor benadering als je als patiënt loot voor de nieuwe behandeling, maar ook toestemming om in de controle groep geloot te worden. In dat geval krijg je dezelfde behandeling als je anders ook zou krijgen en wordt de uitkomst vergeleken met de nieuwe behandeling. Na afloop hoort deze groep dat ze meegedaan hebben aan een studie naar een nieuwe behandeling.

Gedurende 10 jaar krijgen UMBRELLA deelnemers elk halfjaar een samenstelling van verschillende vragenlijsten opgestuurd. Dit zijn bijvoorbeeld vragenlijsten over kwaliteit van leven, fysiek functioneren, cosmetiek (uiterlijk van de borst en tevredenheid daarover), werkvermogen, angst, depressie en klachten van de behandeling. De uitkomst van deze vragenlijsten noemen we patiënt-gerapporteerde uitkomsten. In hoofdstuk 2 wordt gekeken naar de tevredenheid met de cosmetiek van de borst na borstkankerbehandeling. Hoewel borstkankerbehandeling over de jaren verbeterd is, bijvoorbeeld door borstsparende operaties, leidt borstkankerbehandeling onvermijdelijk tot verandering van het uiterlijk van de borst. De studie in hoofdstuk 2 laat zien dat het grootste deel van de patiënten tevreden is met het uiterlijk van de borst na borstkankerbehandeling. Ontevredenheid met het uiterlijk van de borst is geassocieerd met een slechtere kwaliteit van leven, slechter lichaamsbeeld en slechter sociaal en emotioneel functioneren. Het is daarom belangrijk om de cosmetiek na borstkankerbehandeling te evalueren en daarbij te evalueren wat de impact is op kwaliteit van leven. Daarnaast is gebleken dat het belangrijk is om de patiënten voorafgaand aan de behandeling goed te informeren over de mogelijke gevolgen van de behandeling.

Borstkankerbehandeling kan ook effect hebben op het lichaamsbeeld van een patiënt, bijvoorbeeld in hoeverre de patiënt tevreden is met haar eigen lichaam of de ervaring van vrouwelijkheid. In hoofdstuk 3 wordt gekeken naar het lichaamsbeeld van vrouwen in de UMBRELLA studie gedurende de eerste vier jaar na borstkankerbehandeling. Er wordt gezien dat een (hele) kleine groep vrouwen een verminderd lichaamsbeeld heeft, wat mogelijk geruststellend is voor vrouwen die nog aan de borstkankerbehandeling gaan starten. Een verminderd lichaamsbeeld na een jaar is geassocieerd met chemotherapie, een hoger BMI, slechter lichaamsbeeld voorafgaand aan de behandeling en slechter emotioneel functioneren voorafgaand aan de behandeling. Deze patiënten hebben dus mogelijk meer risico op een verminderd lichaamsbeeld. Dit kan de arts helpen om deze patiënten te identificeren en wellicht te informeren voorafgaand aan de behandeling.

Ongeveer twee derde van alle borstkanker patiënten wordt behandeld met radiotherapie. Ondanks een verbetering van de radiotherapie technieken in de afgelopen jaren, is er een risico op late bestralingsschade na radiotherapie. Om het

risico op late bestralingsschade te verkleinen is het belangrijk om te weten welke patiënten meer risico hebben op late bestralingsschade. Daarom is in hoofdstuk 4 een systematisch literatuuronderzoek gedaan naar factoren die geassocieerd zijn met late bestralingsschade. Een hogere dosis radiotherapie (bijvoorbeeld door een extra boost op het tumorbed) of een groter bestralingsvolume is geassocieerd met meer bestralingsschade. Er is geen duidelijke associatie tussen klinische of patiënt-gerelateerde factoren en late bestralingsschade. Dit laat zien dat het belangrijk is om nieuwe radiotherapie technieken te ontwikkelen waarbij bestraald wordt met een lagere dosis of een kleiner volume om zo late bestralingsschade te reduceren. In hoofdstuk 5 is onderzocht wat het effect van late bestralingsschade is op kwaliteit van leven. Binnen het UMBRELLA cohort is een vragenlijst gestuurd die patiënt-gerapporteerde klachten van bestralingsschade evalueert. De meest voorkomende klachten na bestraling is stugheid van de borst en pijn in de borst. Na een mediane follow-up van 38 maanden rapporteerde 16% van de patiënten klachten die passen bij late bestralingsschade. Patiënten met late bestralingsschade rapporteerden vaker een slechter fysiek functioneren, rol functioneren (d.w.z. functioneren bij familie, vrienden of op het werk) en sociaal functioneren in vergelijking met patiënten die geen late bestralingsschade rapporteerden. Nieuwe bestralingstechnieken kunnen late bestralingsschade mogelijk voorkomen. Ook is het belangrijk om behandelingen voor late bestralingsschade te evalueren.

Tot nu toe is het bewijs voor de optimale behandeling van late bestralingsschade schaars. Een van de mogelijke behandelingen is hyperbare zuurstoftherapie. Tijdens hyperbare zuurstoftherapie ademt een patiënt 100% zuurstof in via een masker in een kamer die op hoge druk gebracht wordt. Dit zorgt voor de vorming van nieuwe vaten in de borst, waardoor gebieden die niet goed doorbloed waren door de bestraling weer doorbloed worden. Dit geeft vermindering van klachten. Echter, er is weinig bewijs van de effectiviteit van hyperbare zuurstoftherapie bij late bestralingsschade na borstkanker. In hoofdstuk 6 worden de klachten van late bestralingsschade geëvalueerd in een grote groep borstkankerpatiënten die behandeld is in een centrum voor hyperbare zuurstoftherapie. Voorafgaand aan de behandeling, direct na de behandeling en 3 maanden na behandeling is gekeken welke symptomen van late bestralingsschade de patiënten ervaarden en is kwaliteit van leven geëvalueerd met vragenlijsten. Na hyperbare zuurstoftherapie wordt een significante reductie van pijn, borst- en armsymptomen gezien en verbeterde de kwaliteit van leven. Ook worden er weinig bijwerkingen van de

behandeling gezien. Door het design van de studie konden deze resultaten echter niet vergeleken worden met een controlegroep (d.w.z. een groep patiënten met dezelfde klachten, die geen hyperbare zuurstoftherapie kregen). Daarom is binnen de UMBRELLA studie een gerandomiseerd onderzoek opgezet die hyperbare zuurstoftherapie vergelijkt met een controlegroep. Dit studie design wordt beschreven in hoofdstuk 7. Patiënten in de controlegroep krijgen behandeling met (een combinatie van) oedeemtherapie, fysiotherapie, chirurgie of in sommige gevallen geen behandeling. Dit is behandeling zoals die nu in dagelijkse praktijk ook aan de patiënten gegeven wordt. Drie maanden na hyperbare zuurstoftherapie worden pijnklachten in de borst(wand) vergeleken tussen beide groepen. Ook wordt gekeken naar andere klachten van bestralingsschade, kwaliteit van leven, cosmetiek, en bijwerkingen van de zuurstoftherapie.

De UMBRELLA studie heeft in de afgelopen jaren veel inzicht gebracht in de kwaliteit van leven tijdens en borstkankerbehandeling. Ook heeft het meermalig succesvol gediend als infrastructuur voor gerandomiseerde studies. De studie is in meerdere ziekenhuizen in Nederland geïmplementeerd en we zien dat het percentage dat deelname accepteert hoog ligt (88%). De komende jaren is het de uitdaging voor de UMBRELLA studie om een hoog percentage actieve deelnemers te behouden. Op die manier zullen de deelnemers een representatieve groep blijven vormen voor de algemene borstkankerpopulatie. Momenteel worden de resultaten van de studie alleen gebruikt voor onderzoek. Er kan geëvalueerd worden of de resultaten teruggekoppeld kunnen worden in het elektronisch patiëntendossier, zodat de uitkomsten, zoals kwaliteit van leven, ook zichtbaar zijn voor de artsen in de spreekkamer. Door de UMBRELLA studie op die manier uit te breiden kunnen we de ervaring van patiënten die borstkankerbehandeling gehad hebben, gebruiken om nieuwe patiënten te informeren en behandelingen verbeteren, evenals patiënten individueel monitoren na borstkanker behandeling om zo vroeg in te grijpen als bijvoorbeeld kwaliteit van leven achteruit gaat. Door te leren van elke patiënt kunnen we de borstkankerzorg blijven verbeteren.

Appendices

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List of publications

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Curriculum Vitae

Marilot Batenburg was born on the 3rd of November 1990 in Goirle, the Netherlands. She grew up in a loving family with three younger sisters in Middelburg. After studying linguistics for a year, she started medical school in Utrecht in 2010. During her studies, Marilot has engaged in many extracurricular and social activities, such as the board of the Utrechtse Studenten Hockey Club.

During her fourth year in medical school, Marilot was introduced by Danny Young-Afat and Madelijn Gregorowitsch to the UMBRELLA study group with prof. Verkooijen. The UMBRELLA study design and the goal to improve quality of life of breast cancer patients immediately appealed to her. For that reason she did two more internships under supervision of Lenny Verkooijen, Desirée van den Bongard and Madelijn Gregorowitsch. This resulted in a PhD fellowship supervised by Lenny Verkooijen, Desirée van den Bongard and Wies Maarse immediately after graduating medical school in December 2017. Simultaneously Marilot obtained a post-graduate degree in Epidemiology, specialized in Clinical Epidemiology and Medical statistics and obtained a teaching certificate (basiskwalificatie onderwijs) at the Utrecht University.

In January 2021 Marilot started as a non-training resident Surgery at the St. Antonius hospital in Nieuwegein and Utrecht, where she also supervised the medical interns. After a trip through Europe, she started as a non-training resident internal medicine at the Tergooi hospital. In March 2022 she will start her training for general practitioner in Utrecht.

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