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CLINICAL INVESTIGATION

Patient-Reported Symptoms of Late Toxicity in Patients With Breast Cancer Treated With Hypofractionated Radiation Therapy and the Association With Quality of Life

M.C.T. Batenburg,[*] D.R. Mink van der Molen,[*] F. van der Leij,[*] A. Doeksen,[†] T. van Dalen,[‡] E.J.P. Schoenmaeckers,[§] R.M. Bijlsma,[‖] A.J. Witkamp,[¶] M. Ernst,[#] M.F. Sier,[†,**] W. Maarse,[††] H.J.G.D. van den Bongard,[‡‡] and H.M. Verkooijen,[§§] on behalf of the UMBRELLA study team

[*]*University Medical Centre Utrecht, Utrecht University, Department of Radiation Oncology, Utrecht, the Netherlands;* [†]*St. Antonius Ziekenhuis, Department of Surgery, Nieuwegein, the Netherlands;* [‡]*Diakonessehuis, Department of Surgery, Utrecht, the Netherlands;* [§]*Meander Medisch Centrum, Department of Surgery, Amersfoort, the Netherlands;* [‖]*University Medical Centre Utrecht, Utrecht University, Department of Oncology, Utrecht, the Netherlands;* [¶]*University Medical Centre Utrecht, Utrecht University, Department of Surgery, Utrecht, the Netherlands;* [#]*Alexander Monro Ziekenhuis, Department of Surgery, Bilthoven, the Netherlands;* [**]*Ziekenhuis Rivierenland, Department of Surgery, Tiel, the Netherlands;* [††]*University Medical Centre Utrecht, Utrecht University, Department of Plastic, Reconstructive and Hand Surgery, Utrecht, the Netherlands;* [‡‡]*Department of Radiation Oncology, Amsterdam University Medical Centers, Amsterdam, the Netherlands; and* [§§]*University Medical Centre Utrecht, Utrecht University, Imaging Division, Utrecht, the Netherlands*

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Purpose: Our purpose was to assess the prevalence of patient-reported symptoms of local late toxicity in patients with irradiated breast cancer and determine the association between late toxicity and quality of life.

Methods: Within the prospective Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaluation cohort, a survey on self-reported late toxicity was sent to all patients with breast cancer with ≥12 months interval since radiation therapy treated with curative intent. Patients were treated with hypofractionated radiation therapy of 40 Gy/15 fractions or 42.5 Gy/16 fractions, with or without a simultaneous integrated boost. Symptoms of late toxicity were evaluated on a 4-point Likert scale. Late toxicity was defined as moderate-severe breast or chest wall pain combined with at least 1 other mild-severe late toxicity symptom, that is, breast or arm/hand lymphedema, firmness of the breast, or impaired arm movement. Physical, role, and social functioning were measured before, during, and after the late toxicity survey using the European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire-C30 and compared with a Dutch normative population.

Results: In the study, 1613/2248 patients (72%) were included. Of those, 16% (n = 265) reported late toxicity. The median time interval between radiation therapy and survey was 38 months (interquartile range, 21-55). Moderate/severe firmness of the breast, chest wall pain, and breast pain were reported by, respectively, 18% (n = 295), 14% (n = 225), and 10% (n = 140) of all patients. Physical, role, and social functioning were below the clinical threshold (ie, clinically relevant impairment) in 13% to 52% of patients with late toxicity and 2% to 26% of patients without late toxicity. Patients with late

Corresponding author: M.C.T. Batenburg; E-mail: m.c.t.batenburg@umcutrecht.nl

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M.C.T.B. and D.R.M.v.d.M. contributed equally.

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toxicity significantly more often received analgesics, physiotherapy, and lymphedema therapy compared with patients without late toxicity.

Conclusions: This study provided insight into the prevalence of patient-reported late toxicity after hypofractionated radiation therapy and the influence of late toxicity on quality of life after breast cancer. These results may help health care professionals to inform their patients about long-term effects of breast cancer treatment including hypofractionated radiation therapy.

Introduction

Postoperative radiation therapy plays an important role in breast cancer treatment: it reduces the risk of locoregional recurrence and improves survival.[1,2] However, postoperative radiation therapy in combination with surgery and (neo-) adjuvant systemic therapy also increases the risk of local late toxicity in the years after breast cancer treatment, 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 and the toxicity criteria of the Radiation Therapy Oncology Group are the most commonly used standards by radiation oncologists for evaluating late toxicity.[7,8] However, little is known about patient-reported symptoms of late toxicity in patients treated with hypofractionated radiation therapy for early breast cancer and the effect of self-reported symptoms of late toxicity on quality of life (QoL).

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

Methods and Materials

This study was conducted within the prospective observational multicenter Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaluation (UMBRELLA) cohort study.[9,10] Since 2013, the UMBRELLA study has included patients ≥18 years old, with histologically proven invasive breast cancer or ductal carcinoma in situ 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. For the present study, only patients with at least 1-year follow-up in the UMBRELLA study were included to select patients who finished primary systemic treatment (ie, chemotherapy and/or Human epidermal growth factor receptor 2-targeted therapy). Another reason to include patients with at least 1-year follow-up is that it takes time for late toxicity 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 number 18/399). All patients consented to reuse of their clinical data and patient-reported outcome measurements. Within the UMBRELLA study, tumor and treatment characteristics are provided by the Netherlands Comprehensive Cancer Organization.[11] Smoking and body mass index were collected within the context of the cohort study. Participants who smoked during follow-up in the UMBRELLA study were classified as active smokers. Body mass index 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 toxicity (Supplementary Material 1). Nonrespondents received a reminder after 1 month. The cross-sectional survey was not conducted at a standardized timepoint after radiation therapy, resulting in a variable interval from radiation therapy to assessment of late toxicity. The survey included 13 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), that is, physical, role, and social functioning (ie, functioning in your role around family, friends, or an occupational environment); breast cancer-specific questions concerning arm/shoulder pain, breast symptoms, arm/hand edema; and movement restriction.[12,13] Six additional questions were developed by a radiation oncologist, surgeon, epidemiologist, and hyperbaric oxygen physician. Four of these questions were based on the Common Terminology Criteria for Adverse Events (version 4), the toxicity criteria of the Radiation Therapy Oncology Group, and the EORTC QLQ-C30 and QLQ-BR23 and evaluated to what extent patients experienced breast and/or chest wall pain, firmness of the breast, and satisfaction with cosmetic outcome.[7,8,12,13] All questions were scored on a 4-point Likert scale, that is, "not at all," "a little" (ie, mild), "quite a bit" (ie, moderate), and "very much" (ie, severe). Patients were classified as having late toxicity when they reported moderate to severe breast or chest wall pain in combination with at least 1 other mild to severe late toxicity symptom, that is, breast or arm/hand lymphedema, firmness of the breast, and/or impaired arm movement. The final 2 questions evaluated to what extent patients were able to

wear a seat belt over the clothing of their affected breast and if they received follow-up care after their breast cancer treatment in relation to their complaints.

In the longitudinal UMBRELLA cohort, patient-reported outcomes were collected at regular intervals during and after treatment (ie, 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 toxicity questionnaire was sent in between 2 standard UMBRELLA cohort questionnaires. QoL outcomes, collected by the extra late toxicity questionnaire (T0), were compared with similar outcomes collected by the last filled-out regular UMBRELLA cohort questionnaires up to 6 months before (T - 1) and 6 months after (T + 1) the extra questionnaire.

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 0-100) were calculated in accordance with the EORTC scoring manual.[14] Thresholds for clinical importance were used to evaluate the proportion of patients who experienced clinically relevant impairment in the different QoL domains (83, 58, and 58 for physical, role, and social functioning, respectively).[15] These specific thresholds were established by Giesinger et al[15] to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. EORTC QoL outcomes of the study population were compared with those of a Dutch normative population (n = 727), consisting of women with a comparable age to our study population who had never been diagnosed with cancer.[16] Statistical analyses were performed with IBM Statistical Package for Social Sciences (SPSS) software, version 25.

Results

Of the 3485 patients included in UMBRELLA study by December 2020, 2248 patients were eligible for the present study (Fig. E1). Of those, 1613 patients (72%) responded to the questionnaire and were eligible for analysis. The median age was 58 (range, 24-84) and 99.6% (n = 1606) of the patients were female (Table 1). Most patients (n = 1310, 81%) were treated with lumpectomy (Table 1). The majority (55%) of the patients were treated with hypofractionated radiation therapy of 40 Gy/15 fractions or 42.5 Gy/16 fractions, that is, local/locoregional radiation therapy without boost. When a boost was given (45%), a simultaneous integrated boost was used according to national practice for local and locoregional radiation therapy. The total dose to the tumor bed was 53.4 Gy/20 fractions or 55.9 Gy/21 fractions when a standard boost dose was indicated and 58.75 Gy/22 fractions or 61.2 Gy/23 fractions when a high boost dose was indicated. The median time interval between radiation therapy and the late toxicity survey was 38 months

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

	n = 1613
Gender, n (%)	
Female	1606 (99.6)
Male	7 (0.4)
Age at cohort enrolment, median (range)	58 (24-84)
Highest educational level, n (%)	
Primary or (post-)secondary school	843 (52.3)
College, graduate, or professional degree	716 (44.4)
Unknown	54 (3.3)
Smoking	
Active smoker*	161 (10.0)
Former smoker	711 (44.1)
Nonsmoker	685 (42.4)
Unknown	56 (3.5)
BMI, median (IQR)†	25.5 (5.6)
Unknown, n (%)	63 (3.9)
Pathologic T stadium, n (%)	
0 + IS	262 (16.2)
I	921 (57.1)
II	328 (20.3)
III-IV	35 (2.2)
X + unknown	67 (4.2)
Type of surgery	
Lumpectomy	1310 (81.2)
Mastectomy	158 (9.8)
Mastectomy with direct breast reconstruction	108 (6.7)
Unknown	37 (2.3)
Axillary treatment	
Sentinel node procedure‡	1285 (79.7)
Axillary lymph node dissection	136 (8.4)
No axillary treatment	145 (9.0)
Unknown	47 (2.9)
Systemic treatment§	
Chemotherapy	666 (41.8)
Hormonal therapy	769 (48.3)
HER2-targeted therapy	186 (11.7)
No systemic treatment	617 (38.3)
Unknown	21 (1.3)
Radiation therapy treatment	
Local radiation therapy without boost‖	617 (38.3)

(Continued)

Table 1 (*Continued*)

	n = 1613
Local radiation therapy with boost[¶]	546 (33.8)
Locoregional radiation therapy without boost[#]	275 (17.0)
Locoregional radiation therapy with boost[**]	175 (10.8)
Time interval between radiation therapy and survey in months, median (IQR [max])	38 (21-55 [90])
Time interval between radiation therapy and survey in years, n (%)	
1-2	480 (30.0)
2-4	569 (35.5)
4-6	466 (29.1)
> 6	86 (5.4)

Unless stated otherwise, numbers are shown as n (%). Categories may not sum to a total of 100% because of rounding.

Abbreviations: BMI = body mass index; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; IS = in situ; MARI = marking axillary lymph nodes with radioactive iodine seeds; SIB = simultaneous integrated boost; UMBRELLA, Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaluation.

[*] Active smoking during cohort participation.

[†] Calculated as weight/height^2.

[‡] Including MARI procedure/targeted axillary dissection procedure.

[§] Total percentage >100% as patients may receive a combination of systemic treatment

[‖] 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.

[¶] SIB with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose).

[#] Radiation therapy on periclavicular and/or axillary lymph nodes; 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.

[**] Radiation therapy on periclavicular and/or axillary lymph nodes; SIB with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose).

(interquartile range, 21-55) with a maximum of 90 months. Nonresponders were on average younger (median 53 vs 58 years, respectively) and received lumpectomy (72% vs 81%, respectively) and local radiation therapy with boost (23% vs 31%, respectively) less often in comparison to responders (Table E1). The educational level of the responders was slightly higher compared with the Dutch normative population (44% vs 38%, respectively; Table E1).

Symptoms of skin and subcutaneous tissue toxicity were common: 18% (n = 295) of all patients reported moderate to severe breast firmness, 14% (n = 225) reported moderate to severe chest wall pain (ie, musculoskeletal pain), and 10% (n = 140) reported moderate to severe pain in the breast (Fig. 1). Of all patients, 7% (n = 117) reported moderate to severe lymphedema of the breast. Overall, 265 (16%) patients were classified as having self-reported late toxicity. Moderate to severe chest wall and breast pain were experienced by 79% (n = 210) and 57% (n = 136) of all patients with self-reported late toxicity, respectively, in contrast to 1% (n = 15) and 0.3% (n = 4) in the group of patients without self-reported late toxicity (Fig. E2). In total, 60% (n = 158) of all patients with late toxicity reported moderate to severe symptoms of firmness of the breast in comparison to 10% (n = 137) of the patients classified as having no self-reported late toxicity. After surgery and before radiation therapy, 34.2% (n = 50) of patients with late toxicity experienced moderate to severe breast pain and 23.4% (n = 34) moderate to severe breast edema. Of the patients without late toxicity, 12.4% (n = 94) reported moderate to severe breast pain and 11.4% (n = 87) moderate to severe breast edema after surgery and before radiation therapy.

Patients with self-reported late toxicity received analgesics, physiotherapy, and lymphedema therapy 2 to 8 times more often in comparison to patients without self-reported late toxicity (Table E2). The most common therapy to alleviate symptoms of late toxicity was lymphedema therapy, which was reported by 56% of the patients with late toxicity. Patients with late toxicity were on average younger (53 vs 58 years, respectively; Table 2), more often received chemotherapy (56% vs 39%, respectively) in comparison to patients without late toxicity and more often received ablative surgery with or without immediate breast reconstruction (23% vs 15%, respectively). Patients with late toxicity were on average more often treated with a radiation therapy boost (52% vs 43%, respectively) and locoregional radiation therapy (36% vs 26%, respectively) in comparison to patients without late toxicity.

Patients who received local radiation therapy without boost reported late toxicity less often compared with patients treated with local radiation therapy with boost or locoregional radiation therapy ± boost (12% vs 18%-22%, respectively; Table 3). Mild to severe breast/chest wall pain was reported by 63% to 65% of the patients treated with locoregional radiation therapy with boost compared with 46% to 57% of patients treated with local radiation therapy ± boost or locoregional therapy without boost. A larger proportion of patients who received locoregional radiation therapy with boost reported mild to severe fibrosis in comparison to patients who received local radiation therapy ± boost or locoregional radiation therapy without boost (70% vs 44%-59%, respectively). Mild to severe lymphedema of the breast was experienced by 24% of patients who received local radiation therapy without boost versus 46% of patients who received locoregional therapy with boost.

Almost half of the patients with late toxicity scored below the clinical threshold for physical functioning before, during, and after the late toxicity questionnaire (35%-52%; Fig. 2). The proportion of patients without late toxicity that scored below the clinical threshold for physical functioning (20%-26%) was similar to the normative population (24%) at all 4 time points. At all timepoints, the proportion of patients with late toxicity that scored below the clinical threshold for role functioning was higher in comparison to patients without late toxicity (24%-46% and 7%-22%,

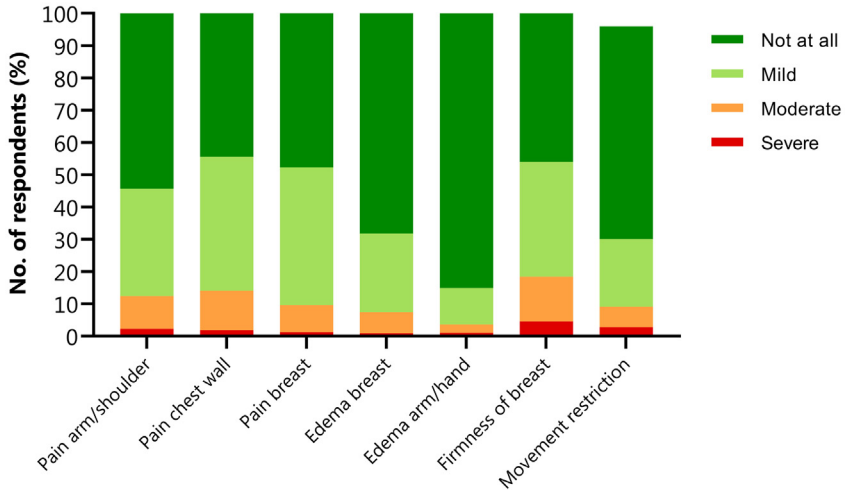

Figure 1. Prevalence of self-reported symptoms of late toxicity in breast cancer patients treated with hypofractionated radiotherapy.

respectively). The proportions of patients with and without late toxicity that scored below the clinical threshold for role functioning were highest at baseline (46% and 22%, respectively) in comparison to the normative population (10%). Patients with late toxicity scored below the clinical threshold for social functioning at all 4 time points (13%-24%) more often in comparison to patients without late toxicity (2%-10%) and the normative population (5%). In addition, mean EORTC scores for physical, role, and social functioning were lower, indicating lower functioning, for patients with late toxicity in comparison to patients without late toxicity and the normative population (Fig. E3).

Discussion

Patient-reported symptoms of late toxicity are relatively common (ie, 16%) in patients treated with hypofractionated radiation therapy for early breast cancer. Of all patients, 18% experienced moderate to severe breast firmness, 10% moderate to severe breast pain, and 7% moderate to severe lymphedema of the breast. The proportion of patients with late toxicity symptoms in the present study is comparable or even lower to that in the Standardisation of Breast Radiation Therapy (START) B trial, in which patients received similar dose fractionation schedules in comparison to our study. After 5 years of follow-up, 10.5% of the patients treated with 40 Gy/15 fractions reported moderate or marked swelling in the area of the affected breast and 38.2% experienced moderate or marked fibrosis.[17,18]

In this observational cohort study, patient-reported outcomes were used to evaluate the prevalence of late toxicity. The rather strict definition of late toxicity, that is, patient-reported moderate to severe breast/chest wall pain in combination with at least 1 other symptom of mild to severe breast firmness, breast edema, or movement restriction, may have underestimated the prevalence of late toxicity to some extent. Our definition, according to which patients were assigned to either the category experiencing or not experiencing late toxicity, can be considered rather arbitrary. However, no standard or validated criteria for late toxicity after radiation therapy were available in the literature to categorize patients. These categories were established to assess the effect of late toxicity on QoL. On average, patients with late toxicity were younger and received a more comprehensive treatment: chemotherapy, mastectomy, and radiation therapy with boost or locoregional radiation therapy. Patients with self-reported late toxicity scored lower in terms of physical, role, and social functioning in comparison to patients without late toxicity. In the group of patients with self-reported late 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 to 3 times higher in comparison to patients without late toxicity. Interestingly, patients with symptoms of late toxicity already reported lower physical, role, and social functioning shortly after breast cancer surgery and before radiation therapy in comparison to patients without late toxicity. Also, a larger proportion of patients with late toxicity already experienced moderate or severe breast pain and breast edema after surgery and before radiation therapy compared with patients without late toxicity. This indicates that breast cancer treatment before radiation therapy, such as surgery and/or neo-adjuvant systemic therapy, might contribute to the inducement of late toxicity symptoms to some extent, such as breast pain, firmness of the breast, and lymphedema. Potentially, (a combination of) breast cancer treatments before radiation therapy might also affect long-term differences in QoL between patients with and without late toxicity. A review by Kuderer et al[19] describes that the burden of chemotherapy-associated adverse events remains high and also affects long-term physical, emotional, and social functioning. As radiation therapy usually follows surgery and/or neo-adjuvant systemic therapy as part of the multidisciplinary breast

Table 2 Patient, treatment, and tumor characteristics of patients with breast cancer with and without self-reported late toxicity

	Late toxicity n = 265	No late toxicity n = 1348
Gender, n (%)		
Female	264 (99.6)	1342 (99.6)
Male	1 (0.4)	6 (0.4)
Age at cohort enrolment, median (range)	53 (26-81)	58 (24-84)
Highest educational level, n (%)		
Primary or (post)secondary school	139 (52.5)	704 (52.2)
College, graduate, or professional degree	113 (42.6)	603 (44.7)
Unknown	13 (4.9)	41 (3.0)
Smoking		
Active smoker*	37 (14.0)	124 (9.2)
Former smoker	114 (43.0)	597 (44.3)
Nonsmoker	101 (38.1)	584 (43.3)
Unknown	13 (4.9)	43 (3.2)
BMI, median (IQR)†	26.6 (6.1)	25.4 (5.4)
Unknown, n (%)	14 (5.2)	49 (3.0)
Pathologic T stadium, n (%)		
0 + IS	50 (18.9)	212 (15.7)
I	130 (49.1)	791 (58.7)
II	66 (24.9)	262 (19.4)
III-IV	9 (3.4)	26 (2.0)
X + unknown	10 (3.8)	57 (4.2)
Type of surgery		
Lumpectomy	197 (73.8)	1114 (82.6)
Mastectomy	34 (12.7)	124 (9.2)
Mastectomy with direct breast reconstruction	28 (10.5)	81 (6.0)
Unknown	8 (3.0)	29 (2.2)
Axillary treatment		
Sentinel node procedure‡	213 (80.4)	1072 (79.5)
Axillary lymph node dissection	26 (9.8)	110 (8.2)
No axillary treatment	19 (7.2)	126 (9.3)
Unknown	7 (2.6)	40 (3.0)
Systemic treatment§		
Chemotherapy	144 (55.6)	521 (39.1)
Hormonal therapy	131 (50.2)	638 (47.9)
HER2-targeted therapy	43 (16.5)	143 (10.7)
No systemic treatment	75 (28.3)	542 (40.2)
Radiation therapy treatment		
Local radiation therapy without boost‖	72 (27.2)	545 (40.4)
Local radiation therapy with boost¶	99 (37.4)	447 (33.2)

(*Continued*)

Table 2 (*Continued*)

	Late toxicity n = 265	No late toxicity n = 1348
Locoregional radiation therapy without boost[#]	55 (20.8)	220 (16.3)
Locoregional radiation therapy with boost[**]	39 (14.7)	136 (10.1)
Time interval between radiation therapy and survey in months, median (IQR [max])	38 (21-55 [85])	38 (21-56 [90])

Unless stated otherwise, numbers are shown as n (%). Categories may not sum to a total of 100% because of rounding. Late toxicity is defined as moderate to severe breast or chest wall pain in combination with at least 1 other mild to severe late toxicity symptom, that is, breast or arm/hand lymphedema, firmness of the breast, and/or impaired arm movement.

Abbreviations: BMI = body mass index; HER2 = Human Epidermal growth factor Receptor 2; IQR = interquartile range; IS = in situ; SIB = simultaneous integrated boost.

[*] Active smoking during cohort participation.

[†] Calculated as weight/height^2.

[‡] Including MARI procedure/targeted axillary dissection procedure.

[§] Total percentage >100%, as patients may receive a combination of systemic treatment

[‖] 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.

[¶] SIB with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose).

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cancer treatment, it remains difficult to assess the exact origin of long-term toxicity after radiation therapy and to evaluate to what extent symptoms of late toxicity can be attributed to radiation therapy itself. The presence of symptoms of late toxicity after radiation therapy therefore should be put into the context of all breast cancer treatments patients have received.

Depending on the symptoms, late toxicity can be treated with analgesics, physiotherapy, lymphedema therapy, or hyperbaric oxygen therapy. These treatments can be time consuming, a burden for patients, and might not always be effective.[20-22] For example, treatment for lymphedema often requires repetitive physical therapy and does not always resolve the symptoms.[21,23] The majority of patients with late toxicity received physical therapy, lymphedema therapy, or analgesics, whereas only 34% 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 toxicity was associated with worse social and role functioning. Possibly, patients with late toxicity are more reserved regarding social interaction. Attention for psychosocial support for patients with late radiation toxicity could be taken throughout and after the course of treatment in order to improve social, emotional and role functioning. These results provide insights into the prevalence of late toxicity and its influence on QoL. These findings may help to adequately inform patients with breast cancer about the expected long-term effects of breast cancer treatment and emphasize the importance of shared decision-making before breast cancer treatment.

It remains important to prevent late toxicity, potentially by individualizing radiation therapy treatment based on risk factors (ie, patient and treatment characteristics) for late toxicity. The prevalence of patient-reported late toxicity in the present study is comparable to or even lower than that in the current literature regarding the prevalence of patient-reported late toxicity after hypofractionated versus conventional radiation therapy. In the UK START B trial, 2215 patients were allocated to radiation therapy with either 40 Gy in 15 fractions over 3 weeks (n = 1110) or 50 Gy in 25 fractions over 5 weeks (n = 1105).[18] Moderate or marked local normal tissue effects, that is, breast induration, breast shrinkage, breast edema, and change in skin appearance, seemed to be lower in patients treated with 40 Gy (n = 526) compared with patients who received 50 Gy (n = 511), with a significantly lower rate for change in skin appearance after radiation therapy with 40 Gy than after that with 50 Gy (P = .02).[18] In the five-fraction radiotherapy for breast cancer-Forward trial, the 5-year prevalence of moderate or marked change in the breast was 32.4% (n = 140) for patients treated with 40 Gy in 15 fractions over 3 weeks.[24] Five years after radiation therapy with 40 Gy/15 fractions, patient-reported moderate or marked firmness of the breast was reported by 14.3% (n = 61) of patients, moderate or marked breast pain by 9.0% (n = 39), and moderate or marked breast edema by 1.5% (n = 7).[24] The prevalence of late toxicity was slightly lower compared with our findings, where moderate or severe firmness was experienced by 18% of patients, breast pain by 10%, and breast edema by 7%. In the present study, an increase in patient-reported symptoms of late toxicity was associated with a radiation boost on the tumor bed or locoregional radiation therapy (Table 3). These findings are in line with the "boost-no-boost" study by Collette et al,[25] where 5318 patients were randomized to receive a 16 Gy boost to the tumor bed in the intervention group or no boost in the control group after whole breast

Table 3 Prevalence of self-reported symptoms of late toxicity in patients with breast cancer per dose fractionation schedule

		Local radiation therapy without boost* (n = 577-617) %	Local radiation therapy with boost† (n = 531-546) %	Locoregional radiation therapy without boost‡ (n = 197-275) %	Locoregional radiation therapy with boost§ (n = 166-175) %
Late toxicity‖	Yes	11.7	18.1	20.0	22.3
	No	88.3	81.9	80.0	77.7
Breast pain	None	54.2	43.7	48.7	37.3
	Mild	39.2	45.8	39.6	48.8
	Moderate	5.5	9.6	10.2	12.0
	Severe	1.0	0.9	1.5	1.8
Chest wall pain	None	49.2	42.7	44.5	34.7
	Mild	40.1	42.9	38.2	45.7
	Moderate	8.9	12.8	14.3	19.1
	Severe	1.8	1.6	2.9	0.6
Shoulder/arm pain	None	61.4	54.6	47.4	39.5
	Mild	27.7	35.8	35.0	42.4
	Moderate	8.8	8.3	13.9	14.5
	Severe	2.1	1.5	3.6	3.5
Fibrosis	None	56.3	41.4	42.3	29.7
	Mild	32.6	38.1	31.6	44.2
	Moderate	8.6	16.0	18.4	18.0
	Severe	2.4	4.4	7.7	8.1
Lymphedema breast	None	75.8	66.4	63.7	54.4
	Mild	18.3	26.5	26.4	36.3
	Moderate	4.9	6.3	8.8	8.8
	Severe	1.0	0.7	1.1	0.6
Lymphedema arm/hand	None	88.9	87.5	76.4	77.9
	Mild	8.0	11.1	16.4	15.7
	Moderate	2.1	0.7	5.8	5.2
	Severe	1.0	0.7	1.5	1.2
Movement restriction	None	73.9	67.2	49.8	58.7
	Mild	19.7	25.6	34.9	26.7
	Moderate	4.9	5.2	9.5	9.9
	Severe	73.9	2.0	5.8	4.7

Categories may not sum to a total of 100% because of rounding.

Abbreviation: SIB = simultaneous integrated boost.

* The dose fractionation schedule of local hypofractionated radiation therapy without boost (including partial breast irradiation) comprises 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.

† The dose fractionation schedule of local hypofractionated radiation therapy with boost comprises SIB with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose).

‡ The dose fractionation schedule of locoregional hypofractionated radiation therapy without boost (including axillary radiation therapy) comprises 40 Gy in 15 fractions or 42.5 Gy in 16 fractions.

§ The dose fractionation schedule of locoregional hypofractionated radiation therapy with boost comprises SIB with a total dose to the tumor bed of 53.4 Gy in 20 fractions or 55.9 Gy in 21 fractions (standard boost dose) or a total boost dose of 58.75 Gy in 22 fractions or 61.2 Gy in 23 fractions (high boost dose).

‖ Late toxicity is defined as moderate to severe breast or chest wall pain in combination with at least 1 other mild to severe late toxicity symptom, that is, breast or arm/hand lymphedema, firmness of the breast, and/or impaired arm movement.

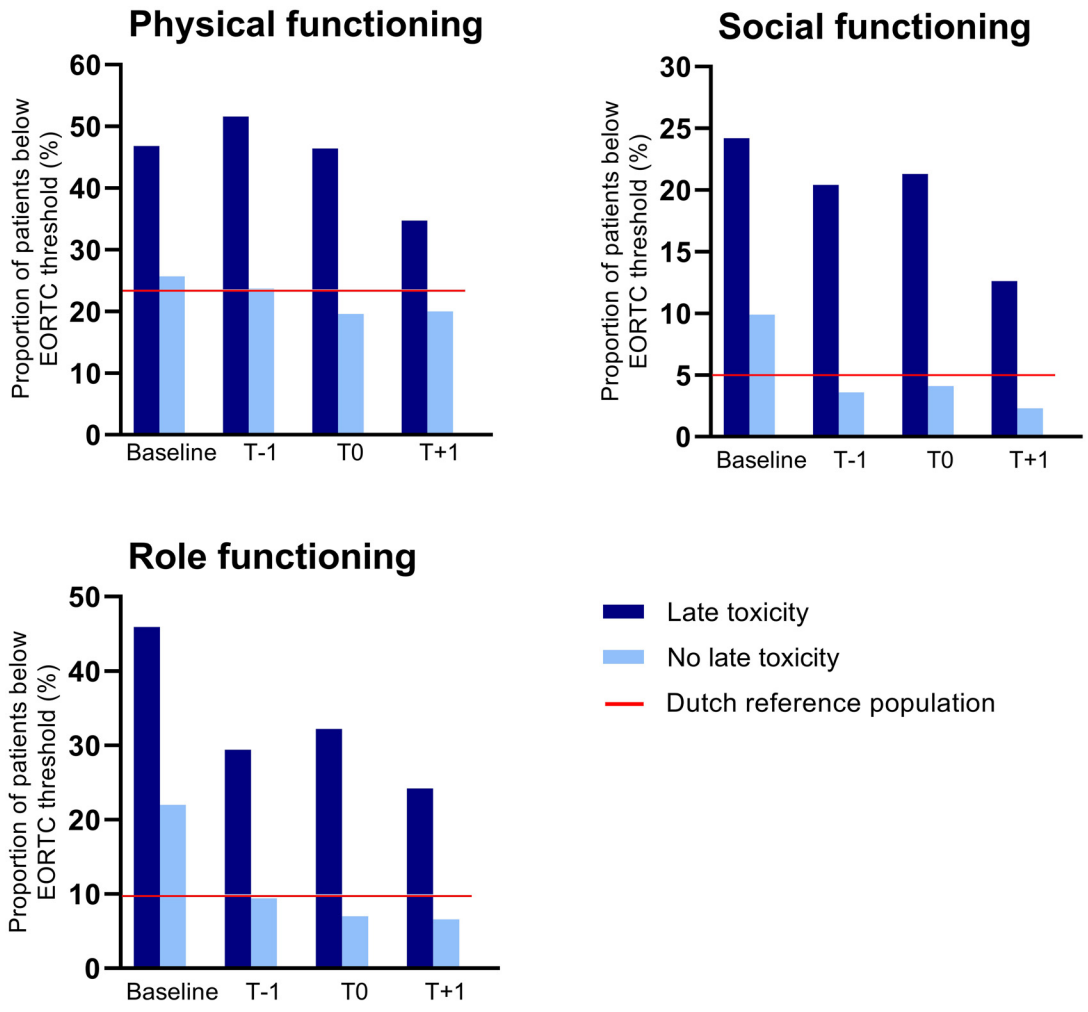

Figure 2. Proportion of irradiated breast cancer patients with and without self-reported symptoms of late toxicity who function below the clinical relevant EORTC QLQ-C30 thresholds immediately after surgery/prior to radiotherapy (ie, baseline), prior to, during and after the late toxicity questionnaire in comparison to a Dutch normative population.
Time: Baseline = upon cohort inclusion/start radiotherapy; T-1 = standard UMBRELLA-cohort questionnaire up to six months before the late toxicity questionnaire; T0= at the moment of the late toxicity questionnaire; T+1= standard UMBRELLA-cohort questionnaire up to six months after the late toxicity questionnaire
The Dutch normative population comprised 727 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 (15).

irradiation of 25 × 2 Gy.[25] At 10 years after breast cancer treatment, the risk of fibrosis significantly increased with increasing maximum whole breast irradiation dose and with concomitant chemotherapy ($P < .01$).[25] The study by Whelan et al,[26] where 1832 women with node-positive or high-risk node-negative breast cancer were randomized to undergo either whole-breast irradiation with regional nodal irradiation or whole-breast irradiation alone, observed significantly more lymphedema, telangiectasia of the skin, and fibrosis in the group treated with regional nodal irradiation.[26] These results emphasize the importance of treatment de-escalation, such as omitting a boost dose in patients with low-risk breast cancer or even omitting radiation therapy treatment, if possible.[27]

The findings of the current study should be interpreted in the context of its limitations. Even though the response rate was high, selective nonresponse cannot be ruled out. Potentially, patients who fully participate in the (longitudinal) UMBRELLA cohort may experience a higher QoL.[16] Consequently, the proportion of patients with late toxicity may have been underestimated. EORTC QLQ-C30 questionnaires were completed immediately after breast cancer surgery and before radiation therapy. Therefore, information about (breast) symptoms and QoL before surgery and neoadjuvant systemic treatment is lacking. Consequently, it is impossible to determine whether symptoms of late toxicity result in lower QoL, or if patients with lower QoL before breast cancer treatment experience a higher burden of late

side effects in the years after breast cancer treatment. The aim of this cross-sectional study was to evaluate both prevalence of late toxicity and factors associated with late toxicity in a large real-world breast cancer cohort treated with hypofractionated radiation therapy. Controlling for the baseline differences regarding QoL was therefore not performed. In the present observational cohort study, patient-reported outcomes were used to evaluate prevalence of late toxicity. Although symptoms of late toxicity could not be confirmed through clinical assessment, this current study gives insight into the overall patient experience of symptoms of late toxicity through real-world data of a large cohort of patients with breast cancer. Postoperative complications, such as infections, are known risk factors for the development of late toxicity but were not assessed in the present study.[28] Finally, the late toxicity questionnaire used for this study was sent once to all eligible patients in the cohort. Symptoms of late toxicity, such as fibrosis or breast and chest wall pain, may change over time.[29] Symptoms of late toxicity were only measured at one point in time in the present cross-sectional study. Therefore, the time interval for the development of late toxicity and how the self-reported symptoms of late toxicity develop over time remain unclear.

Conclusions

Patient-reported symptoms of late toxicity are relatively common in patients treated with hypofractionated radiation therapy for early breast cancer, with a prevalence of 16%. The most common self-reported late toxicity symptoms among patients with irradiated breast cancer are breast and chest wall pain (10%-14%) and firmness of the breast (18%). Patients with self-reported symptoms of late toxicity receive additional care aimed at reducing late toxicity, such as analgesics, physiotherapy, and lymphedema therapy 2 to 8 times more often compared with patients without late toxicity. On average, patients with late toxicity were younger and received a more comprehensive treatment: chemotherapy, mastectomy, radiation therapy with a boost, or locoregional radiation therapy. Late toxicity is associated with reduced physical, role, and social functioning even before the start of hypofractionated radiation therapy. The combination of breast cancer treatments makes it impossible to determine the exact origin of the late toxicity symptoms. A multidisciplinary approach to treat and reduce late treatment toxicity is therefore important. This study may help health care professionals to inform their patients about the long-term effects of breast cancer treatment.

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