Original Article

Changes in acute and late toxicity and patient-reported health-related quality of life following radiotherapy in women with breast cancer: A 1-year longitudinal study

ABSTRACT

Objective: The objective of this study was to investigate the frequency of acute and late toxicities, as well as changes in the quality of life (QOL) for breast cancer patients following radiotherapy (RT).

Materials and Methods: A total of 108 breast cancer women were recruited for this prospective study. Data were collected at various intervals; prior to, and 1, 3, 6 months, and 1 year after radiation therapy. The primary outcomes were toxicity radiation therapy oncology group/European Organization for Research and Treatment of Cancer (EORTC) criteria. Our secondary outcome was QOL, measured using EORTC QLQ-C30 and Edmonton Symptom Assessment Scale. We employed Friedman's two-way analysis to evaluate the changes in QOL over the course of 1 year.

Results: The early toxicities that are most commonly experienced include pharyngeal, skin, and mucous membrane toxicity. Late toxicities frequently involve skin and submucosal toxicity. To measure patient functionality, all functional subscale scores except for the patient's emotional state increased over time compared to pre-RT. Symptoms of the patients, which were included in the QOL symptom scale, decreased during the follow-up period, except for fatigue; however, changes in pain, insomnia, and loss of appetite did not significantly change. We identified the analogous symptom profiles in Edmonton. Although patients' overall health scores declined in the 1st and 3rd months after radiotherapy (RT), they rebounded at 6 and 12 months.

Conclusion: For breast cancer patients, RT did not adversely affect functional capacity or exacerbate symptoms, but persistent fatigue did increase during the observation period. Health-care professionals ought to devise strategies to assist patients with skin toxicity and fatigue.

Keywords: Breast cancer, health-related quality of life, radiotherapy, toxicity

INTRODUCTION

Breast cancer is the most common type of cancer and the second cause of cancer-related deaths.[1] Cancer treatments aim not only to ensure the survival of the patient but also to increase the quality of life (QOL).[2] Hence, in recent years, early diagnosis and adjuvant treatments have increased the life expectancy of these patients, which in turn has highlighted the importance of QOL.[3] With an increased emphasis on patient-centered care, health-related QOL and other patient-reported outcomes that quantify how a patient feels or functions are assuming a more prominent role as important endpoints in cancer clinical trials.[4]

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Radiotherapy (RT) is an important and well-validated treatment option for breast cancer patients at all clinical stages. Breast-conserving surgery (BCS) has been the most common surgical method in recent years. Radiotherapy is the definitive standard treatment, especially in early-stage breast cancer patients due to its positive effect on survival and local recurrence after BCS.[5] Therefore, the widespread use of RT means a rapid increase in the number of patients experiencing treatment-related side effects. Thus, meta-analyses that show RT reduces death from breast cancer and increases overall survival, it has taken its place alongside surgery and chemotherapy.[6] Radiotherapy, as a treatment method, has some side effects as well as its strengths.

The acute adverse effects of RT include weakness, pain, skin reactions, esophagitis, dysphagia, swelling in the breast, sore throat, and armpit hair loss.[7] The most common adverse late effects include permanent skin discoloration, breast tissue thickening, fibrosis, telangiectasia, lung damage, dry cough, change in the appearance of the breast, lymphedema, brachial plexopathy, and increased rib brittleness.[7,8] In particular, radiodermatitis is one of the symptoms that negatively affects the QoL.[9,10] Although these side effects are primarily related to the dose and technique, patient-related factors also play an important role.[11]

Patient QOL assessments have many benefits. These include accurately explaining to patients and health-care team members how treatments affect functioning and general well-being, identifying common problems, and interventions for these problems. In addition, explaining the relation between RT's side effects and QOL could guide the development of future interventions across different cancer types and a greater QOL measure.

To improve the QoL in these patients, there is a need for more information about RT's side effects, their prevalence, and the effects on these patients' health. Although various studies have already been conducted on quality-of-life in patients with breast cancer, research focused on both radiotherapy toxicity and QoL longitudinally is limited. In this context, the results of the study will make significant contributions to the limited knowledge on the subject. The purpose of this study was to identify the changes and interrelationships in the radiotherapy-induced early and late symptoms among breast cancer patients, as well as their impact on the QoL after therapy. The research questions are: (1) What is the prevalence of acute and late radiotherapy-induced toxicities? and (2) What is the change in QOL in breast cancer patients after radiotherapy?

MATERIALS AND METHODS

Ethical considerations

This study was conducted according to the ethical standards of the responsible committee on human experimentation and the Declaration of Helsinki. Ethical approval was given by the Ethics Committee of the Scientific Research Faculty of Medicine (number 24237859-88) on January 29, 2018. Before collecting the data, the researcher informed the patients about the purpose, method, and scope of the scientific research, and their written consent was obtained.

Patients

The study was conducted between Mach 2018 and January 2020. This descriptive and prospective study consisted of 108 patients with breast cancer who had undergone RT for 1 year. Patients with primary breast cancer and a life expectancy of more than 1 year and who could read and speak Turkish were included. Patients who have communication difficulties and visual/hearing/speech impairment are excluded. Additional exclusion factors were women who were unable to undergo medical follow-up for geographical, social, or psychological reasons. Since these stages were adjusted according to the control times in the hospital and the patients were called by phone, there was no data loss in the study. The Open Epi program was used to calculate the strength of the study, and an 85.6% confidence interval (CI) was determined.

Treatment regimen

Target and organ at-risk volume delineation was performed according to the ASTRO and ESTRO guidelines.[12,13] The RT dose to the breast, chest wall, axillary lymph nodes, and supraclavicular fossa was 50 Gy (25 fractions × 2 Gy), given over 5 weeks, with five irradiations every week after mastectomy. In BCS patients, an additional dose applied to the tumor bed was 60–66 Gy. The goal of the prescription was to ensure that 95% of the volume was receiving 95% of the prescribed dose. All patients were treated with a 6 MV linear accelerator (Electa-Clinac).

Follow-up and outcomes

Patients were assessed before RT (baseline assessment; T^1), one (T^2), three (T^3), six (T^4), and 12 months (T^5) after radiotherapy respectively.

Toxicity criteria of the radiation therapy oncology group

The first author, who is a radiation oncologist, assessed acute and late toxicities using the toxicity criteria of the Radiation Therapy Oncology Group (RTOG). This scale consists of two parts: Acute and late toxicity. Each part was evaluated on

a scale of zero (no symptoms) to five (tissue death directly related to the effect of radiation). We also assessed acute toxicity after one (T^2), and late toxicity after 3, 6, and 12 months later radiotherapy.

Quality of life scale – Turkish version 3

QOL scale consists of three dimensions and 30 questions on general well-being, functional difficulties, and symptom control. This scale evaluates physical function, role performance, emotional, cognitive, and social state, general well-being, symptom control, body appearance, sexual function and satisfaction, future anxiety, and treatment-related side effects. A high functional and overall health status and a low symptom scale score indicate a high QoL. The scale was developed by the European Organization for Research and Treatment of Cancer QOL (EORTC QLQ-C30-version 3) and validated in Turkey, and Cronbach's alpha coefficient was 0.914.[14] In our study, this coefficient was 0.884. We assessed QoL for each time point.

The Edmonton Symptom Scale

EORTC has a QLQ-C30 symptom subscale. However, the total score of this subscale cannot be calculated. We wanted to investigate both the frequency of symptoms not found in EORTC QLQ-C30 and to determine the effect of symptoms on the overall QOL. For this purpose, we used the Edmonton Symptom Assessment Scale. In 1991, Edmonton *et al*. developed a scale to evaluate the nine symptoms commonly experienced by patients with cancer.[15] These include pain, fatigue, nausea, sadness, anxiety, insomnia, anorexia, well-being, and shortness of breath, among others. The severity of each symptom was numerically evaluated on a scale of zero to ten. The validity and reliability of the scale were evaluated by Kurt and Ünsar in 2009 in Turkey, and Cronbach's alpha reliability coefficient value of 0.83 was determined.[16] In our study, this coefficient was 0.873. We used it at each time point.

Statistical analysis

IBM SPSS version 22.0 software (IBM SPSS Corp., Armonk, NY, USA) was used to analyze the data. The normality of the sample means of the scores was verified using the Kolmogorov–Smirnov test. For secondary outcomes, statistical analyses were performed using the repeated-measures analysis of variance Friedman's two-way analyses. All statistical tests were conducted at the 0.05 significance level (2-sided).

RESULTS

Table 1 depicts some demographic and clinical characteristics of patients. The number of patients who had BCS and mastectomy was equal. Before radiotherapy, 81.5% of the patients received chemotherapy.

The most common acute toxicities after 1 month of radiotherapy were pharyngeal dysphagia (87.0%), skin (66.5%), and mucous membrane (55.4%) [Table 2 and Figure 1]. Table 3 represents late radiation toxicities after 3, 6, and 12 months of radiotherapy. Figure 2 shows symptoms for 1 year according to the Edmonton Symptom Diagnostic Scale. The most common symptoms experienced by patients were the changes in skin and nails (4.6 ± 3.6) 1 month after RT. Patients reported concern and sadness at each time point 3 months later after RT ($P < 0.001$).

Table 1: Participant's demographic and clinical characteristics (*n*=108)

Characteristics	Mean±SD/*n* (%)
Age	51.3±12.8
Marital status	
Married	97 (89.8)
Single	11 (10.2)
Education level	
Primary and below	53 (49.0)
Secondary	12 (11.1)
High school	25 (23.1)
University	18 (16.8)
Cancer stage	
Stage 1	36 (33.3)
Stage 2	38 (35.2)
Stage 3	34 (31.5)
Type of surgery	
BCS	54 (50.0)
Modified radical mastectomy	54 (50.0)
Chemotherapy	
Yes	88 (81.5)
No	20 (18.5)
Comorbidity	
Yes	43 (39.8)
No	65 (60.2)

SD: Standard deviation, BCS: Breast-conserving surgery

Table 2: Acute radiation toxicity (*n*=108)

Toxicity	Grade	T^2, *n* (%)
Pharyngeal dysphagia	Grade 1	47 (43.5)
	Grade 2	47 (43.5)
Skin	Grade 1	41 (37.9)
	Grade 2	29 (26.8)
	Grade 3	2 (1.8)
Mucous membrane	Grade 1	50 (46.2)
	Grade 2	10 (9.2)
Larynx	Grade 1	30 (27.7)
	Grade 2	5 (4.6)
Lung	Grade 1	3 (2.7)
Heart	Grade 1	18 (16.6)

T: Time (2: 1st after month RT). RT: Radiotherapy

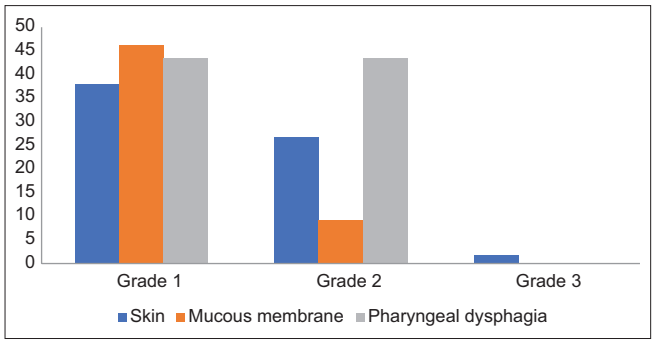

Figure 1: The most common three acute toxicities after 1 month of RT

Table 3: Late radiation toxicity (*n*=108)

Toxicity	T[3], *n* (%)	T[4], *n* (%)	T[5], *n* (%)
Skin			
Grade 1	32 (29.6)	33 (30.5)	30 (27.7)
Grade 2	62 (57.4)	27 (25.0)	-
Grade 3	14 (13.0)	48 (44.4)	-
Subcutaneous tissue			
Grade 1	49 (45.3)	29 (26.8)	54 (50.0)
Grade 2	52 (48.1)	67 (62.0)	-
Grade 3	-	12 (11.2)	-
Mucous membrane			
Grade 1	64 (59.2)		
Grade 2	40 (37.0)		
Lung			
Grade 1	27 (25.0)		

T: Time (1: After RT, 2: 1st after month RT, 3: 3st after month RT, 4: 6st after month RT, 5: 12st after month RT). RT: Radiotherapy

Detailed information about the symptoms is found in the table in Table 4.

Table 5 presents the results of repeated measurements using Friedman's five time points. We determined that the patient's functional status subscales scores increased over time. In addition, the difference between all subscale scores except emotional function was significant at time points ($P < 0.05$). Except for pain, insomnia and loss of appetite, the change in the mean of subscales over time was significant ($P < 0.05$). Except for fatigue, symptom subscale scores decreased over time [Table 5]. Global scale scores decreased in the first 3 months after RT and then increased significantly at 6 and 12 months. We determined that the change in the global health of the patients in each measurement was significant except for the last measurement.

DISCUSSION

This study verified alterations in early and late toxicities triggered by radiotherapy while examining their effect on patients' QOL on year posttreatment. As far as we are aware, this is one of the few studies to prospectively evaluate

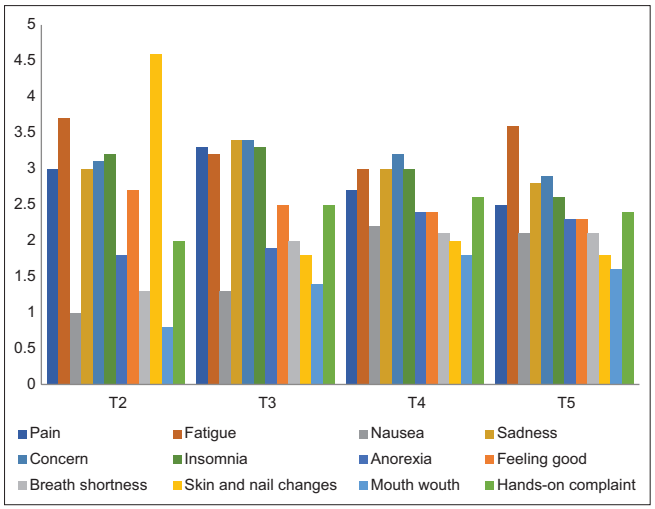

Figure 2: Changes in patient's Edmonton symptoms at follow-up

the variations in QoL of breast cancer patients by utilizing the EORTC QLQ-C30 apparatus and examining RT-related toxicities prior to, during, and after RT. The article by Marta *et al*.[17] asserts that there has been insufficient investigation into the QOL of breast cancer patients who have undergone RT treatment.

In our study, we found that the most commonly reported symptoms 1 month after radiotherapy were pharyngeal dysphagia and toxicity in the skin and mucous membranes. Skin toxicity, or radio dermatitis, is the most commonly reported undesirable side effect of breast cancer radiotherapy during the acute period, as demonstrated by previous studies.[18-20] However, our research shows a difference from the literature: Pharyngeal toxicity was actually more prevalent than skin toxicity. To determine toxicity in radiodermatitis studies, various tools were employed including RTOG and other scales, such as those found in studies.[20-22] It is plausible that differences in toxicity assessment tools contributed to our results. In addition, the frequency and early period issues during radiation therapy may vary depending on the treatment volume, device, and planning technique, as cited in reference.[19] Therefore, skin toxicity is influenced by the various risk factors such as large breast volume, smoking habits, and body mass index.[23] The differences in participants' risk factors may have contributed to the early onset of toxicity observed in our study. Although this was not the study's primary objective, we did not investigate the potential impact of risk factors on toxicity.

Six months after radiotherapy, we found late toxicity only in the skin and subcutaneous tissue. These late toxicity results were similar to previous studies.[19,24,25] The systematic review that investigated the results of the study in which the skin

Table 4: Some symptoms during the one-year follow-up

Symptom	Mean±SD					*F*	*P*
	T^1	T^2	T^3	T^4	T^5		
Pain	2.3±2.4	3.0±2.7	3.3±2.3	2.7±1.4	2.5±1.5	490.38	<0.0001
Fatigue	3.6±3.0	3.7±2.8	3.2±2.1	3.0±1.7	2.6±1.5	531.65	<0.0001
Nausea	3.2±2.5	1.0±1.8	1.3±1.7	2.2±1.5	2.1±1.8	296.59	<0.0001
Sadness	3.0±3.1	3.0±2.8	3.4±2.4	3.0±1.7	2.8±1.5	425.17	<0.0001
Concern	2.8±3.1	3.1±3.0	3.4±2.3	3.2±1.8	2.9±1.7	425.92	<0.0001
Insomnia	3.0±3.5	3.2±2.7	3.3±2.6	3.0±1.6	2.6±1.4	425.51	<0.0001
Anorexia	2.0±2.8	1.8±2.0	1.9±1.5	2.4±1.3	2.3±1.6	458.35	<0.0001
Feeling good	3.3±2.9	2.7±2.2	2.5±1.5	2.4±1.3	2.3±1.6	644.56	<0.0001
Breath shortness	1.7±2.6	1.3±2.2	2.0±1.9	2.1±1.3	2.1±1.7	288.55	<0.0001
Changes in skin and nails	3.0±3.5	4.6±3.6	1.8±1.7	2.0±1.3	1.8±1.4	349.15	<0.0001
Wound in mouth	1.5±2.6	0.8±2.1	1.4±1.7	1.8±1.4	1.6±1.4	235.70	<0.0001
Hands-on complaint	2.4±3.3	2.0±2.8	2.5±0.2.1	2.6±1.6	2.4±1.8	378.63	<0.0001

Table 5: Patient's quality of life scores changes in follow-up (n=108)

	Mean±SD					*P*	Friedman analysis
	T^1	T^2	T^3	T^4	T^5		
Functional status							
Physical function	61.1±26.4	61.9±25.2	66.9±22.9	70.6±21.8	71.6±20.0	0.000	T^1, T^2<T^4
Emotional function	60.3±22.4	61.7±23.9	65.0±21.2	65.7±23.9	68.6±25.9	0.102	No difference
Cognitive function	64.4±28.6	61.7±25.0	64.6±22.7	65.5±25.2	74.3±25.7	0.004	T^1<T^4
Role function	60.9±24.0	61.7±25.9	66.2±23.6	76.9±28.6	76.0±25.2	0.001	T^1<T^4, T^5–T^2<T^4, T^5
Social function	64.3±25.7	61.8±24.8	64.1±20.7	71.9±20.9	78.2±25.8	0.000	T^1<T^3, T^4, T^5–T^2<T^4
Symptoms							
Fatigue	37.4±23.9	40.7±25.4	35.6±21.5	44.3±26.6	47.2±21.7	0.001	T^1>T^3, T^5
Pain	37.1±24.2	37.6±25.3	38.8±23.8	42.5±27.7	34.2±22.5	0.063	No difference
Nausea and vomiting	37.0±25.6	37.3±24.7	23.4±26.2	17.5±29.7	21.2±29.3	0.001	T^1, T^2, T^3>T^4, T^5
Insomnia	37.4±24.8	37.5±26.9	40.9±26.7	38.0±24.6	33.6±26.7	0.489	No difference
Appetite loss	31.4±27.8	36.9±22.7	27.0±26.6	29.3±27.6	28.0±21.6	0.117	No difference
Constipation	34.5±24.6	38.5±27.6	24.3±25.2	20.3±25.2	28.0±24.0	0.001	T^2>T^4, T^5–T^3>T^4
Financial difficulties	50.0±23.1	41.0±23.1	34.2±22.0	24.0±26.1	25.0±22.6	0.001	T^1>T^4, T^5–T^2>T^4, T^5–T^3>T^5
Dyspnea	35.9±26.2	41.2±27.1	28.3±25.7	26.8±28.9	20.4±21.1	0.000	T^1, T^4, T^5–T^2>T^4
Global health	64.6±17.3	60.5±24.9	37.7±11.4	58.1±24.9	60.8±24.5	0.001	T^1, T^2>T^3–T^3<T^4

T: Time (1: After RT, 2: 1st after month RT, 3: 3st after month RT, 4: 6st after month RT, 5: 12st after month RT). SD: Standard deviation, RT: Radiotherapy

changes after radiotherapy were evaluated ultrasonically revealed skin thickening and edema.[26]

We conducted a study investigating the change in patients' QOL before and 1 year after radiotherapy (RT). Six months following RT, we observed a decrease in symptoms and an improvement in global health and functional status. In other words, while no significant change in QOL occurred in the first 3 months after RT, improvement began thereafter. Most research on radiotherapy and QOL focuses on type, dosage, and their impact on well-being. Radiotherapy can cause considerable side effects that can diminish the QOL for cancer survivors.[27] Additional studies explore the influence of various variables such as exercise, yoga, and education on patients' QOL. Marta *et al*.[17] conducted a review of 182 studies investigating the impact of radiotherapy on the QOL of individuals with breast cancer. They discovered that 18 of these studies provided significant advantages for the QoL, while all 13 trials found no discrepancies in the QoL between the study groups. Furthermore, other systematic reviews of Asian women with breast cancer yielded comparable findings to Marta's *et al.* research on QoL.[17,28,29] Research findings indicate similarities. Our study reveals an increase in the QOL over time postradiotherapy. Patients' recovery after treatment is time-consuming, and the reduction in symptoms affects this process.

However, there was no significant improvement or deterioration in emotional status, pain, insomnia, or appetite loss during this period. This outcome indicates that while other symptoms are improving, these symptoms are not. In other words, patients continue to experience these symptoms at a comparable level for 1 year after RT. Montazeri indicated that psychological factors predicted the

subsequent QOL or even overall survival in breast cancer patients.[30] In previous systematic reviews, there have been reports of declining emotional well-being, increased depression and anxiety across the different stages of treatment and disease progression.[28,31] Our study also found that symptoms of sadness, concerns, and insomnia were prevalent in patients 1 year after radiotherapy, according to the Edmonton scale. These symptoms are known to be associated with emotional well-being. Again, Montazeri discovered that distress, anxiety, and depression were prevalent among breast cancer patients even years after the diagnosis and treatment of the disease.[30]

We found fatigue did not change in time, as measured by the Edmonton scale. Despite this, it remained the symptom with the highest severity rating. On the other hand, results were observed within the QoL symptom subscale, whereby all symptoms with significant changes decreased over time, except for fatigue, which actually increased. This difference between the two measurement tools may depend on the number of questions in the measurement tools. According to these results, we can say that the QOL scale is more reliable in determining fatigue in cancer patients. A meta-analysis showed a noteworthy reduction in the occurrence of severe fatigue, which appeared to transpire in the initial 6 months following the completion of treatment.[32] After RT, 27.3% of patients with breast cancer had pain, as suggested by a prevalence study.[33] A systematic analysis, which looked at cancer patients, emphasized that approximately 47%–49% of survivors experience financial troubles.[34] In some literature, these financial dilemmas are referred to as "financial toxicity." Financial toxicity is the most robust autonomous predictor of low QOL in cancer survivors owing to the costs of cancer care.[35-37] Nonetheless, financial difficulties were reduced over time in this study. This variation may arise from the health insurance policies in the countries where the research was conducted.

Limitations

This study is noteworthy as a longitudinal study, although it has certain limitations. The research results should be interpreted with caution due to the sample size. Prior to radiotherapy (RT), surgical treatment was performed on all patients, and the majority also underwent chemotherapy. Consequently, issues such as skin-nail changes and fatigue cannot be solely attributed to RT, unlike radio dermatitis and other specific problems. A limitation of this study is that it relies on patient characteristics. Surgical treatment, chemotherapy, radiotherapy volumes (chest wall, breast, axillary lymph node, and supraclavicular lymph node area), and treatment technique variations may influence the QOL outcomes in a biased manner.

CONCLUSION

This prospective longitudinal study provides a unique perspective regarding the relationship between RT toxicities and QOL. Our findings indicate that early toxicities among breast cancer patients frequently resulted in pharynx, skin, and mucosa toxicities, with late toxicity primarily affecting the skin and subcutaneous tissue. Despite radiation therapy, there did not appear to be significant worsening of patients' functional status, except for emotional status over time. However, patients reported experiencing consistent levels of emotional status, sadness, anxiety, and insomnia for up to a year. As patients who have completed radiotherapy typically spend their time at home, health-care professionals must develop strategies to provide emotional and toxicity support during the first 6 months. In addition, future research ought to concentrate on validating and outlining the origins of patients' challenges and proposing remedies. Permanent solutions need to involve adjustments in regulations regarding ensuring patients and establishing and negotiating fees. However, immediate interventions should target the oncologist and the patient. Executing a comparable study with a more significant sample would bolster the study's outcomes. In addition, a comparative study considering patients who received chemotherapy before RT versus those who did not would be beneficial. Subsequent research should evaluate the efficiency of prompt and practical symptom screening techniques, as well as the approaches used for their management. Studies can be conducted comparing the QOL of patients who received and did not receive RT within the same time period after diagnosis. In addition, conducting this study in a multicenter manner will ensure the generalizability of the results.

Patients with breast cancer who undergo RT experience treatment-related issues, which can have a negative impact on their QOL. Gaining comprehensive data on the prevalence, severity, and symptoms of these problems would aid in creating preventative or mitigating strategies. Currently, research examining the relationship between QOL and toxicity for breast cancer patients following radiotherapy is limited, so these findings could help to address this gap in the literature. This study will contribute to understanding how patients' symptoms affect their QOL and to develop effective treatment and care approaches accordingly.

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Conflicts of interest

There are no conflicts of interest.

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