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Research Article

The impact of acute radiodermatitis on quality of life in breast cancer patients receiving conventionally fractionated versus hypofractionated breast irradiation

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Abstract

Background: Although prior studies have examined the effect of radiation-induced skin toxicity on patients' Quality of Life (QOL), little is known about the effect of radiotherapy on skin-related QOL with different radiotherapy schedules.

Objective: To assess the impact of radiodermatitis on the quality of life in patients undergoing conventionally fractionated versus hypofractionated radiation therapy for breast cancer.

Methods: We conducted a prospective study including breast cancer patients undergoing radiotherapy. Patients were evaluated at the initial visit, weekly during radiotherapy and 2 weeks after the end of treatment. Radiodermatitis was graded weekly using Common Terminology Criteria of Adverse Events (CTCAE) version 4.0. Patient reported symptoms of pain or itching were also assessed on Visual Analogue Scale (VAS). The Skindex-16 QOL instrument was administered at 1 week of initiation and 2 weeks after the completion of radiotherapy.

Results: Thirty patients completed the study and received either Conventional Radiotherapy (CRT) (15 patients) or Hypofractionated Radiotherapy (HRT) (15 patients). A total of 16 patients (53.3%) developed grade 1 radiodermatitis and 3 (20%) developed grade 2 throughout the study. All patients receiving HRT had their radiodermatitis cleared at the end of treatment, while 9 patients (60%) had persistent radiodermatitis after CRT. Lower pain scores were reported with HRT than with CRT. Patients in the HRT group reported better QOL scores for symptom and emotion domains at 2-week follow-up compared to baseline while no significant change was found in any of domain scores after CRT.

Conclusion: Our results demonstrated the advantage of HRT in improving RD and patient reported discomfort in breast cancer patients compared to CRT. A beneficial effect for HRT was also noted in the improvement of patients' QOL particularly in the symptom and emotional domains. Therefore, it is important to include patient QOL measures when evaluating patients undergoing radiotherapy so that the treatment approach can be modified to improve QOL.



Introduction

Radiodermatitis (radiation dermatitis) is a common side-effect of radiation therapy for breast cancer [1]. It is estimated that 85–95% of patients experience some degree of radiodermatitis during the course of breast cancer radiotherapy [2–4]. These radiation skin reactions often lead to itching and pain, delays in treatment, and decreased aesthetic appearance and subsequently affect the patient's quality of life and well-being [5,6]. Novel technologies and treatment schedules have been successful in the amelioration, but not the elimination, of these adverse side effects [7].

Qualitative research and review articles have suggested that radiodermatitis may be experienced by patients as itching, sensitivity, pain, numbness, tenderness, warmth, tingling, throbbing, tightness, heaviness, and burning [8,9] and that skin pain may be associated with fatigue, body image disturbance, sleep problems, and emotional distress [10,11]. Such qualitative data suggest that in order to understand the impact of radiodermatitis on quality of life, it is critical to assess not only the occurrence of skin reactions, but also patients' subjective experience of such reactions [12]. Over the past few years, Patient-Reported Outcomes (PROs) have become common instruments to aid in accurate assessment and management of various symptoms [13].

In particular, the Skindex-16 has been used to study the effects of a wide variety of skin conditions on patients' lives. It is a 16-item self-administered survey instrument developed by Chren, et al., [14] and can be used to assess how patients progress over time or after therapies [15]. This tool has been increasingly used in patients with skin toxicities resulting from their anti-cancer treatment [16,17].

The present study aimed to assess the effect of radiodermatitis on the quality of life of patients undergoing radiation therapy for breast cancer with respect to radiotherapy schedule.

Patients and methods

Patient selection and randomization

The study population was selected from consecutive patients attending the Department of Clinical Oncology, Assiut University hospital during the period from December 2016 to September 2018 and included breast cancer patients receiving adjuvant radiotherapy after surgery.

Eligible patients were women with histologically confirmed carcinoma of the breast who underwent surgical intervention and were going to receive radiation therapy. Routine staging procedures were completed prior to enrolment.

Exclusion criteria were pregnancy, breast feeding, concomitant chemotherapy, previous radiotherapy to the treated area, patients with other skin conditions, including atopic dermatitis, psoriasis and ichthyosis. Adjuvant chemotherapy was given before radiotherapy according to guidelines [18].

Initially, 37 patients were invited to participate in the study. Seven patients were lost to follow up and excluded from the study.

The study was approved by the Ethics Committee of Faculty of Medicine, Assiut University, and informed consent was obtained from all patients prior to enrolment. The study was conducted in accordance with principles of the Declaration of Helsinki.

Radiotherapy schedules

Following breast surgery, patients received local radiotherapy to the breast and chest wall +/- lymph nodes either as Conventional Radiotherapy (CRT), 2Gy in 25 fractions to a total dose of 50Gy, or Hypofractionated Radiotherapy (HRT) with 2.65Gy in 16 fractions, to a total dose of 42.50Gy, five times a week. The radiation energy was generated by a linear accelerator (Varian dnx Clinac 2300C); the energy used is 6Mv.

Patients were instructed to apply a thin layer of a topical moisturizer twice a day to the irradiated area from the start of radiotherapy and continuing every day during the radiotherapy period and for two weeks after the completion of radiotherapy.

Clinical assessment and follow-up

For all patients, a full medical history was obtained and demographic data collected, including age, previous use of oral contraceptives, medical diseases, family history and menopause. Patients were assessed at baseline immediately prior to the initiation of radiation therapy and weekly thereafter throughout radiotherapy and finally at 2weeks after its completion.

Radiation dermatitis on the irradiated breast was assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [19].

Radiation associated symptoms of pain and itching were reported weekly during radiotherapy and 2weeks after radiotherapy was finished using a visual analogue scale (VAS) (10cm in length, 0=no symptoms, 10=worst possible symptoms).

Quality of life assessments using Skindex-16 questionnaire were performed at the first week of radiation therapy and at the end of a 2-week observation period after radiotherapy. Skindex-16 is a 16-item skin-specific QOL instrument [14]. It comprises three scales to assess patient symptom, emotion and functioning. Item responses are standardized from 0 (no effect) to 100 (maximal effect). The Egyptian Arabic version of the questionnaire has been validated in a previous study [20].

Statistical analyses

Statistical analyses were performed with SPSS version 22. Chicago, Illinois (Statistical Package for Social Sciences). Data were described using mean \pm SD and proportions. The qualitative measures were compared by the chi-square test or



Fisher's exact test, as appropriate. For quantitative measures Student's t-test or Mann-Whitney test was used to calculate differences between the treatment arms. Post-treatment values were compared with the pretreatment baseline by the paired t-test or Wilcoxon-signed Rank test in both treatment arms. Spearman's rank Correlation test was used to assess the correlation between between Skindex-16 scores and radiodermatitis grade, pain and itching scores. Uni-variate analysis of factors that may be associated with increased radiation dermatitis was also determined. P-value considered statistically significant when $P < 0.05$.

Results

Baseline characteristics of the studied patients

Of the 37 enrolled patients, 30 female patients with breast cancer completed the study. Their mean age was 49.17years, 16% had diabetes mellitus and 20% had hypertension. Positive family history was found in 2 patients. Among patients, 3(10%) had used oral contraceptives and 18(60%) had menopause. The most common tumor histology was infiltrating ductal carcinoma (86%). Twenty nine patients (96.7%) had primary breast cancer and one (3%) patient had recurrent breast cancer. The staging of breast cancer ranged from T1-4, N0-

3. The patients were previously treated surgically either with modified radical mastectomy (80%) or with breast-preserving surgery (20%). Twenty-four patients (80%) received lymph node radiation.

Regarding the type of radiotherapy, 15 patients (50%) received Conventional Radiotherapy (CRT) and 15 patients (50%) received Hypofractionated Radiotherapy (HRT). There were no significant differences between the CRT and HRT groups with respect to age, systemic diseases, use of contraceptives, family history, radiation dose, pathology of tumor, or type of surgery ($p > 0.05$) (Table 1).

Ten patients (66.6%) in the CRT group and 9 patients (60%) in the HRT group developed clinical signs of radiodermatitis. All these patients had grades 1-2 radiodermatitis, with no patients developing more than grade 2. The incidence of radiodermatitis was not significantly different between the two groups as evident by the maximum grade of radiodermatitis encountered throughout all the study period ($p = 0.809$). However, at the end of treatment, 9 patients (60%) had persistent radiodermatitis in the CRT group, all of them had grade 1, while radiodermatitis resolved in all patients in HRT group at the end of treatment ($p < 0.001$).

Table 1: Baseline characteristics of the study groups.

	Conventional radiotherapy (CRT) (n=15)		Hypofractionated radiotherapy (HRT) (n=15)		P-value	Total	
Age (years) Mean± SD	50.24±10.07		44.52±11.79		0.066	49.17±10.07	
Diabetes Mellitus, n (%)							
Yes	3	(20)	2	(13.3)	1.000	5	(16.7)
No	12	(80)	13	(86.7)		25	(83.3)
Hypertension, n (%)							
Yes	5	(33.3)	1	(6.7)	0.169	6	(20)
No	10	(66.7)	14	(93.3)		24	(80)
Oral contraceptives, n (%)							
Yes	1	(6.7)	2	(13.3)	1.000	3	(10)
No	14	(93.3)	13	(86.7)		27	(90)
Family history, n (%)							
Positive	2	(13.3)	0	(0)	0.483	2	6.7
Negative	13	(86.7)	15	(100)		28	93.3
Menopause, n (%)							
Pre-menopause	4	(26.7)	8	(53.3)	0.136	12	(40)
Post-menopause	11	(73.3)	7	(46.7)		18	(60)
Breast cancer, n (%)							
Primary	15	(100)	14	(93.3)	1.000	29	(96.7)
Recurrent	0	(0)	1	(6.7)		1	(3.3)
Breast side, n (%)							
Right	9	(60)	7	(46.7)	0.464	16	(53.3)
Left	6	(40)	8	(53.3)		14	(46.7)
Pathology, n (%)							
Infiltrating ductal carcinoma	14	(93.3)	12	(80)	0.475	26	(86.7)
Infiltrating lobular carcinoma	0	(0)	1	(6.7)		1	(3.3)
Mixed	1	(6.7)	2	(13.3)		3	(10)
Surgical procedures, n (%)							
Modified radical mastectomy	13	(86.7)	11	(73.3)	0.651	24	(80)
Breast-preserving surgery	2	(13.3)	4	(26.7)		6	(20)
Lymph node radiation, n (%)							
Yes	11	(73.3)	13	(86.7)	0.651	24	(80)
No	4	(26.7)	2	(13.3)		6	(20)



All patients in the CRT group developed pain during radiotherapy, while pain was found in 5 patients (33.3%) only in HRT group ($p < 0.001$). Itching was experienced in 2 patients (13.3%) and 7 patients (46.7%) in the CRT and HRT groups respectively ($p = 0.109$).

The maximum pain scores were also higher with CRT compared to HRT ($p = 0.005$). In addition, higher mean pain scores were also found in CRT group than HRT group at the end of treatment ($p = 0.014$). There was no significant difference between the two radiotherapy groups regarding maximum itching scores or itching scores at the end of treatment (Table 2).

There was no significant difference between HRT and CRT groups regarding the mean baseline skindex-16 scores at the first week ($p = 0.13$) or at the end of treatment ($p = 0.467$). Both groups showed no significant change in the mean overall skindex-16 scores after treatment compared to the baseline scores. Significant decrease in mean skindex-16 symptom and emotional domain scores from baseline was detected in the HRT group, while functional domain showed no significant change at the end of treatment. In the CRT group, no significant change in any of the three domain scores was found at the end of treatment (Table 3). Skindex-16 scores showed significant positive correlation with pain scores ($r = 0.424$, $p = 0.020$), but no significant correlation was detected between skindex-16 scores and radiodermatitis grade ($r = 0.167$, $p = 0.379$) or itching scores ($r = 0.268$, $p = 0.153$).

On comparing patients who developed radiodermatitis with those who didn't develop radiodermatitis throughout the sessions, no significant relation was found regarding age, type of surgery, use of oral contraceptives and presence of diabetes mellitus or hypertension with the development of radiodermatitis (Table 4). These factors also had no influence on the persistence of radiodermatitis at the end of treatment (Table 5).

Discussion

Radiation dermatitis is a common sequela of radiotherapy

Table 2: Radiodermatitis grades, pain and itching scores in the two treatment groups.

	Conventional Radiotherapy (CRT) (n=15)		Hypofractionated Radiotherapy (HRT) (n=15)		P-value
	No.	%	No.	%	
Radiodermatitis grade (last week)					<0.001
Grade 0	6	40.0	15	100.0	
Grade I	9	60.0	0	0.0	
Grade II	0	0.0	0	0.0	
Maximum radiodermatitis grade:					0.809
Grade 0	5	33.3	6	40.0	
Grade I	8	53.3	8	53.3	
Grade II	2	13.3	1	6.7	
Pain score last week	3.50±2.24	4.0(1.0-7.0)	1.93±3.45	0.0(0.0-9.0)	0.014*
Maximum pain score	4.67±2.94	5.0(1.0-9.0)	1.93±3.43	0.0(0.0-9.0)	0.005*
Itching score last week	2.13±1.92	1.0(0.0-6.0)	2.29±3.50	0.0(0.0-9.0)	0.310
Maximum itching score	3.53±3.29	2.0(0.0-9.0)	2.93±3.86	1.0(0.0-10.0)	0.310

Table 3: Mean skindex-16 scores at 1st week and at 2week- follow up after radiotherapy in the two treatment groups.

Skindex-16 domain scores	Conventional radiotherapy (CRT) (n=15)	Hypofractionated radiotherapy (HRT) (n=15)	P-value
	Mean± SD	Mean± SD	
Symptom (W1)	28.05±17.85	21.66±30.38	0.057
Symptom (2W- follow up)	29.72±25.44	14.72±23.14	0.031*
P-value	0.975	0.028*	
Emotion (W1)	33.33±26.24	27.93±21.48	0.678
Emotion (2W- follow up)	31.74±24.57	17.61±13.25	0.134
P-value	0.529	0.025*	
Functional (W1)	34.44±30.85	33.55±34.92	0.817
Functional (2W-follow up)	32.22±30.46	33.78±35.59	0.785
P-value	0.526	1.000	

p-value 1: CRT versus HRT.

p-value 2: comparison of mean values at different weeks with week 1 values in each group.

Table 4: Relationship between clinical variables and development of radiodermatitis.

	No radiodermatitis (n= 11)		Radiodermatitis (Grade 1-2) (n= 19)		P-value
Age, Mean±SD	50.09±10.77		48.63±9.90		
Surgical procedures, n (%)					0.641
Modified radical mastectomy	8	(72.7)	16	(84.2)	
Breast-preserving surgery	3	(27.3)	3	(15.8)	
Diabetes Mellitus					0.626
Yes	1	(9.1)	4	(21.1)	
No	10	(90.9)	15	(78.9)	
Hypertension					1.000
Yes	2	(18.2)	4	(21.1)	
No	9	(81.8)	15	(78.9)	
Oral contraceptives					1.000
Yes	1	(9.1)	2	(10.5)	
No	10	(90.9)	17	(89.5)	

Table 5: Relationship between clinical variables and persistence of radiodermatitis at the 2week -follow up after radiotherapy.

	No radiodermatitis (n=17)		Persistent radiodermatitis (n=13)		P-value
Age, Mean± SD	48.53±10.27		50.00±10.15		
Surgical procedures, n (%)					0.196
Modified radical mastectomy	12	(70.6)	12	(92.3)	
Breast-preserving surgery	5	(29.4)	1	(7.7)	
Diabetes Mellitus					0.628
Yes	2	(11.8)	3	(23.1)	
No	15	(88.2)	10	(76.9)	
Hypertension					1.000
Yes	3	(17.6)	3	(23.1)	
No	14	(82.4)	10	(76.9)	
Oral contraceptives					0.565
Yes	1	5.9%	2	15.4%	
No	16	94.1%	11	84.6%	

for breast cancer patients and often significantly impacts patients' quality of life. In our study, we assessed whether the radiation schedule can modify QOL in breast cancer patients receiving radiotherapy. HRT showed an advantage in improving the outcome of radiodermatitis compared to CRT. Although both



types of radiation did not show significant difference in the incidence of radiodermatitis, HRT was associated with higher rate of clearance of radiodermatitis at the end of treatment and lower pain scores. This is in agreement with previous studies showing less skin toxicity and less subjective symptoms in patients receiving HRT compared to those receiving CRT [21,22].

Our findings demonstrated that the negative impact of radiodermatitis on QOL could be partly reversed with HRT, as evident by improved Skindex-16 scores for the symptom and emotion domains, which was not observed with CRT schedule.

A previous analysis of Quality of Life (QOL) outcomes from the START (Standardisation of Breast Radiotherapy) trials revealed a lower rate of patient-reported moderate to marked breast, arm, and shoulder symptoms in patients randomized to HF-WBI [23].

However, they used general health QOL assessment measure and thus their responses may be dominated by the underlying disease and other co-therapies. Therefore, the skindex-16 was specifically selected for use in this study since it was designed to measure skin-related QOL allowing more reliable interpretation of the impact of radiodermatitis on skin-related QOL of patients according to radiotherapy schedule.

The results of our study showed a negative impact on the overall QOL of patients from the first week of radiation and after completion of radiotherapy as measured by total skindex-16 scores. Significant improvement in the symptom and emotional domain skindex-16 scores at the end of treatment was found only in the patients receiving HRT, suggesting its efficacy in reversing the negative impact of radiation dermatitis on QOL. This might be related to the clearance of radiodermatitis and pain amelioration that were observed in patients receiving HRT.

A previous study used skindex-16 to assess the QOL of patients before the initiation and after completion of radiotherapy for a variety of tumors. They showed worsening of QOL after radiotherapy which was greatest in the symptom domain followed by the emotional domain. However, they did not assess the effect of radiotherapy schedule on QOL [24]. Other studies also showed symptoms and feelings domains to be significantly influenced by radiodermatitis and were related to radiation dermatitis grade [25,26].

Fuzissaki, et al., [25] used Dermatology Life Quality Index (DLQI) questionnaire in evaluating the influence of the degree of radiodermatitis and showed a negative impact on the general QOL of patients presenting with severe radiodermatitis (grade 3 and 4), where domains of symptoms and feelings, daily activities, leisure, work and school also presented a statistically significant difference, according to the degree of radiodermatitis and the evaluation timing of radiotherapy. Their results indicated that there was a negative impact on QOL of women with breast cancer throughout radiotherapy, with the greatest impact coming from severe radiodermatitis.

In our study, no patients developed severe radiodermatitis grades (G3-4) which may explain the lack of correlation between radiodermatitis grade and skindex-16 scores. In contrast, a previous study showed all measures of skin-related QOL (using DLQI) significantly worsened at the fifth week of radiotherapy compared to baseline. However, their findings could be due to that radiodermatitis was expected to peak at 5 weeks and they didn't assess skin-related QOL after the end of radiotherapy [26].

In the current study, we found no effect for age, type of surgery or comorbid conditions (diabetes mellitus and hypertension) on the occurrence of radiation dermatitis or its persistence after treatment. Our results are in accordance with Pommier, et al., [27], who showed that type of surgery was not a significant prognostic factor for radiation skin toxicity. In contrast, another study [28], found that type of surgical treatment and radiation field may affect the severity of radiation skin reactions.

Previous studies also suggested that older age and comorbid conditions as diabetes or renal failure might be risk factors for developing skin reactions [29]. Although skin type has been hypothesized to influence radiation dermatitis [28], a number of studies [30,31], showed that skin type does not affect the susceptibility to radiodermatitis. In our study, the majority of patients were of the same skin type (III-IV) and so the effect of skin type was not evaluated.

The present study has some limitations including the relatively small number of patients studied and the lack of long-term assessment. Further long-term studies with large number of patients are recommended for more conclusive information.

In conclusion, the results of this prospective study showed that radiotherapy had a negative impact on QOL of women with breast cancer, with a greater impact in those receiving CRT, especially on the symptom and emotional aspects. The results of the present study allow a better understanding of the experiences of radiodermatitis from the patients' point of view as well as its impact on QOL. Skin-related QOL can provide specific information on the effects of approaches to manage local radiodermatitis symptoms. Management approaches directed to minimize the impairment in QOL need to be adopted to help patients get through the radiotherapy.

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