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Research Article

Skin toxicity investigation in breast cancer patients undergoing radiation therapy

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This study has investigated skin toxicity in breast cancer patients undergoing radiation therapy. The study was conducted in 1401 at a radiation therapy center in Yazd city and included 30 patients who have undergone radiation therapy using conventional and hypofractionation methods, and in which the whole or part of the breast has been exposed to radiation. Skin complications of grade skin toxicity during treatment and within 40 days after radiotherapy have been evaluated in both methods. Results have shown that four people (26.6%) have had grade three and six people (40.0%) have had grade two skin toxicity, with conventional treatment having caused more skin complications compared to hypofractionation, which has caused fewer skin toxicity without reducing efficacy. Additionally, the ratio of skin toxicity in the conventional technique has been higher than in the hypofractionation technique after 40 days of radiation therapy. The study has concluded that hypofractionation has resulted in less skin toxicity than conventional treatment.

KEYWORDS

Breast cancer, Radiation therapy, Hypo fractionation, Conventional, Skin toxicity.

I. INTRODUCTION

Cancer is one of the most common causes of death worldwide, and its incidence is increasing day by day in different societies. Radiation therapy is one of the most common and effective methods for cancer treatment. This method can be used alone or in combination with other treatment methods such as surgery, chemotherapy, or hormone therapy [1].

The main goal of radiation therapy is to deliver maximum damage to the tumor while causing minimal damage to the healthy tissues surrounding it. Therefore, in treatment design, the priority is to apply the maximum dose to the tumor while considering the dose limitations of the organs at risk (OARs) surrounding it. However, the unavoidable doses to non-targeted organs and tissues can occur in radiation therapy [2,3].

Given the importance of radiation therapy in cancer treatment, precise planning by radiation oncologists, medical physicists, and radiation therapy technologists is very important. In addition, investigating the problems and side effects associated with radiation therapy is of great importance. For example, in radiation therapy for breast cancer, problems can include skin reactions, breast swelling, changes in breast shape and color, sensitivity in the nipples, and effects on the heart and lungs. Therefore, a thorough evaluation of the side effects and problems associated with radiation therapy is crucial [4,5]. These complications affect important parameters such as psychological status, quality of life, the patient's immune system, as well as the course of the disease, and even the patient's lifespan [6]. According to the common toxicity criteria of the Radiation Therapy Oncology Group (RTOG), skin toxicities are classified into the following groups based on toxicity criteria (Table 1) [7].

Hypofractionation and conventional techniques are two radiation therapy methods for breast cancer. In hypofractionation, a higher dose is given to the patient, but the number of treatment sessions is fewer. For example, in hypofractionation, 15 to 16 treatment sessions are required for the patient, while in conventional therapy, more than 25 treatment sessions are needed. The goal of using hypofractionation is to reduce treatment time and improve the quality of life for patients. Additionally, with a higher dose per session, the tumor is treated with a higher dose of radiation therapy. In conventional therapy, a lower dose is given to the patient, but more treatment sessions are required. However, conventional therapy is still one of the main methods for treating breast cancer. Other differences include the possible side effects. Generally, hypofractionation may cause fewer side effects such as fatigue, skin burns, and pain. In contrast, conventional therapy may cause more side effects such as fatigue, skin changes, and pain. However, the side effects of both techniques may vary in each patient and may be different due to the patient's characteristics, the type of cancer, and the treatment conditions [8,9].

Table **1** common toxicity criteria of the Radiation Therapy Oncology Group [7].

Grade	**Change**
Grade 0	No change
Grade 1	Mild erythema, dry skin, mild sweating, and hair loss
Grade 2	Moderate erythema, moist desquamation in skin folds and creases, and moderate edema
Grade 3	: Moist desquamation outside of skin folds and creases, bleeding due to minor trauma or abrasion
Grade 4	Necrosis, full-thickness skin ulceration, spontaneous bleeding
Grade 5	Death

Alongside treatment strategies and the impact of techniques on treatment efficiency, radiation therapy requires precise treatment planning, which is carried out by a radiation oncologist, radiation therapy physicist, and radiation therapy technologists. Treatment planning is one of the most critical stages in effective treatment [10].

A study was conducted in 2020 by Julie et al. to compare the acute toxicity and quality of life between hypo-fractionated and conventional radiation therapy for breast cancer. Acute skin toxicity and quality of life were evaluated at baseline and at weeks 2, 4, 6, and 8 after the start of treatment for a subgroup of patients. Acute skin toxicity was similar between the groups at baseline but was lower with hypofractionation compared to conventional treatment at the end of the 8 weeks. Hypofractionation led to an improvement in overall quality and quality of life, which was attributed to a reduction in skin and breast side effects and improved attractiveness [11]. The purpose of this study was to investigate skin reactions in breast cancer patients undergoing radiation therapy using two techniques: hypofractionation and conventional fractionation. Given the severe skin reactions that occur in some breast cancer patients after receiving radiation therapy, this study was conducted to reduce skin and breast side effects and improve patient outcomes. For this purpose, skin reactions were evaluated in both the hypofractionation and conventional fractionation groups of breast cancer patients from the beginning of treatment. The results of the study showed that using hypofractionation can lead to a reduction in skin reactions in breast cancer patients undergoing radiation therapy. Therefore, this study has provided valuable insights into the use of hypofractionation to mitigate skin and breast side effects in breast cancer patients undergoing radiation therapy.

II. MATERIAL AND METHODS

In this research, the 30 breast cancer patients were analyzed cross-sectionally in the year 1401. Patients who met the inclusion and exclusion criteria and provided informed consent were enrolled in the study. The patients who had pre-existing skin problems, skin lesions, shingles, lupus, eczema, or prior radiation exposure were excluded from the study. Before the start of radiation therapy, the skin condition of each patient was evaluated by a specialist physician at the radiation therapy center, and skin toxicity was assessed during treatment and within 40 days after radiation therapy. In this study, the patients were examined using both conventional fractionation and hypofractionation methods. In the conventional fractionation method for breast cancer radiation therapy, a total dose of 5000 cGy was prescribed in 25 fractions, along with a boost dose of 1000 cGy in 5 fractions. In the hypofractionation method, a total dose of 4250 cGy was prescribed in 16 fractions, with a boost dose of 1000 cGy in 5 fractions. Considering that grade 2 occurred more frequently in patients, the significance was checked for grade 2. Average, standard deviation, frequency, and frequency percentage indicators were used for description. To check the difference between the two groups, the $\chi 2$ test with a value of $\alpha=0.05$ was used. All analyses were performed in SPSS software version 24, with a significance level of 5%.

III. RESULT

The frequency of qualitative demographic variables is listed in Table 2 for patients with conventional treatment. The highest age of the participants in this study in conventional treatment was a 77-year-old woman and the youngest was a 28-year-old woman. 10 people (66.7%) of cancer patients in the right breast, 10 people (66.7%) had a history of chemotherapy and 6 people (40.0%) had a history of cancer in the family. The maximum body mass index (BMI) of the patients was between 25 and 29.9.

Table 2 Clinical characteristics of patients with conventional treatment.

Variable	frequency (percentage)
Age	
20-35	2 (13.3)
36-50	6 (40.0)
51-70	5 (33.3)
71>0	2 (13.3)
Breast	
Left	5 (33.3)
Right	10 (66.7)
History of cancer in the family	
Yes	6 (40.0)
No	9 (60.0)
BMI	
18.5<0	0 (0.0)
18.5-24.9	2 (13.3)
25-29.9	9 (60.0)
30-39.9	4 (26.7)
Chemotherapy	
Yes	10 (66.7)
No	5 (33.3)

The frequency of qualitative demographic variables is listed in Table 3 for patients with hypofractionation treatment. The oldest participant in this study receiving hypofractionation treatment was a 69-year-old woman and the youngest was a 33-year-old woman. Six patients (40.0%) had cancer in the right breast, nine patients (60.0%) had a history of chemotherapy, and five patients (33.3%) had a family history of cancer. The maximum body mass index (BMI) of the patients was between 25 and 29.9.

Table 3 Clinical characteristics of patients with hypofractionation treatment.

Variable	frequency (percentage)
Age	
20-35	1 (6.7)
36-50	2 (13.3)
51-70	12 (80.0)
71>0	0 (0.0)
Breast	
Left	9 (60.0)
Right	6 (40.0)
History of cancer in the family	
Yes	5 (33.3)
No	10 (67.7)
BMI	
18.5<0	0 (0.0)
18.5-24.9	4 (26.7)
25-29.9	9 (60.0)
30-39.9	2 (13.3)
Chemotherapy	
Yes	9 (60.0)
No	6 (40.0)

The frequency and percentage of skin complications in breast cancer patients with conventional and hypofractionation methods are shown in Table 4. The data is presented at intervals of one week during treatment and 40 days after treatment, and the statistical difference between these two methods is also shown. As can be seen, in both radiation therapy methods, skin complications occurred from the second week, and no incidence of grade 4 skin complications was observed.

In conventional radiotherapy, the highest incidence of grade 1 skin toxicity occurred during the third and fourth weeks of treatment (93.3% and 66.6%, respectively). The highest incidence of grade 2 toxicity occurred in week 6 (66.6%) and the highest incidence of grade 3 toxicity also occurred in week 6 (26.7%). Forty days after radiotherapy, grade 1 skin toxicity had the highest incidence compared to other grades (53.3%).

In hypofractionation radiotherapy, the highest incidence of grade 1 skin toxicity occurred during the third week of treatment (80.0%). The highest incidence of grade 2 toxicity occurred in week 4 (40.0%). There was no incidence of grade 3 or higher during or 40 days after radiotherapy. Forty days after radiotherapy, grade 1 and grade 0 skin toxicity had the highest incidence compared to other grades (46.7%).

IV. Discussion

Many studies have been conducted on the comparison of skin complications in hypofractionation and conventional treatments for breast cancer patients undergoing radiation therapy.

In a 2019 study by Schmeel et al., the frequency and severity of radiation-induced acute skin reactions during hypofractionated versus conventional whole-body irradiation were investigated. The results showed that the severity of radiation therapy dermatitis in patients receiving hypofractionation was significantly lower compared to conventional therapy. Grade zero radiation dermatitis occurred in 21.43% versus 4.28% of patients following WBI hypofractionation and conventional therapy, respectively. Grade ≥2 dermatitides occurred in 27.14% versus 42.91%, and grade ≥3 dermatitides occurred in 0% versus 4.4% of patients following WBI hypofractionation and conventional therapy, respectively [12]. Another study by Reshma was conducted to investigate the difference in acute toxic effects of radiation therapy for the breast between conventional and hypofractionation treatment programs. The study found that patients receiving conventional treatment experienced more skin damage compared to those receiving hypofractionation treatment [13].

Table 4. The frequency of skin complications in CFRT and HFRT treatment and the statistical differences in the incidence of grade 2 skin complications between two radiation therapy methods at different times from the beginning of radiation therapy to 40 days after radiation therapy.

	Frequency - HFRT				**Frequency - CFRT**				
	Grade				Grade				**P-value****
Time (Week)	0	1	2	3	0	1	2	3	
1	15 (%100)	0 (%0)	0 (%0)	0 (%0)	15 (%100)	0 (%0)	0 (%0)	0 (%0)	**-**
2	14 (%93.3)	1 (%6.7)	0 (%0)	0 (%0)	14 (%93.3)	1 (%6.7)	0 (%0)	0 (%0)	**-**
3	3 (%80.0)	12 (%20.0)	0 (%0)	0 (%0)	1 (%6.7)	14 (%93.3)	0 (%0)	0 (%0)	**0.02**
4	1 (%6.7)	8 (%53.3)	6 (%40.0)	0 (%0)	0 (%0)	10 (%66.7)	5 (%33.3)	0 (%0)	**0.51**
5	0 (%0)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	5 (%33.3)	7 (%46.7)	3 (%20.0)	-
6	0 (%0)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	1 (%6.7)	10 (%66.7)	4 (%26.6)	-
Forty days*	7 (%46.7)	7 (%46.7)	1 (%6.7)	0 (%0)	5 (%33.3)	8 (%53.3)	2 (%13.4)	0 (%0)	**0.01**
Total	15 (%100)	14 (%93.3)	6 (%40)	0 (%0)	15 (%100)	14 (%93.3)	6 (%40.0)	4 (%26.6)	**0.01**

*Forty days after treatment

**Statistical differences comparing grade 2 skin toxicity in two radiation therapy techniques

A study conducted in 2015 showed that skin complications were less frequent in patients receiving hypofractionation treatment compared to conventional treatment. In this study, 50 breast cancer patients were divided into two groups and received hypofractionation and conventional radiation therapy, respectively, with a radiation dose of 42.5 Gy. The results indicated that patients in the hypofractionation group experienced fewer skin complications than those in the conventional group [14].

A 2017 study showed that skin complications were similar between patients receiving hypofractionation and conventional treatment.

In this study, 107 breast cancer patients were divided into two groups and received either hypofractionation or conventional radiation therapy. The results showed no significant difference in skin complications between the two treatment groups [15]. A 2021 study showed that there was no significant difference in skin complications between patients receiving hypofractionation and conventional treatment. In this study, 90 breast cancer patients were divided into two groups and received either hypofractionation or conventional radiation therapy. The results showed that there was no significant difference in skin complications between the two treatment groups [16].

In this study, according to Table 4, the skin complications were assessed during and forty days after treatment. It was determined that four people (26.6%) had grade three and six people (40.00%) had grade two skin complications in total. The results showed that conventional treatment caused more grade three skin complications than hypofractionation treatment, without causing any additional complications. Furthermore, the incidence of skin complications 40 days after radiation therapy was higher in the conventional technique compared to the hypofractionation technique.

Based on the results reported in the studies, no clear conclusion has been reached regarding which treatment method (hypofractionation or conventional) causes fewer skin complications in breast cancer patients undergoing radiation therapy. To draw more accurate conclusions about this comparison, additional studies with larger sample sizes and similar designs are needed.

Among the limitations of this study are the short duration of the study and the lack of follow-up of patients for a long time after the end of treatment, the limitations in performing skin tests and evaluating skin complications due to safety and health restrictions during the COVID-19 pandemic, and the limitations in following up with patients after the end of treatment due to restrictions on movement and face-to-face communication.

V. Conclusion

In this research, the possibility of comparing conventional and hypofractionation treatments in the treatment of breast cancer patients was investigated. The results showed that the occurrence of skin complications in conventional treatment is more than in hypofractionation. However, to determine the effect of dose interruption on the damage caused to the skin and other sensitive organs, more experimental studies and longer-term follow-ups of patients are needed to investigate the dosimetry factors and the relationship between the two different cross-sectional methods. Finally, according to the obtained data, the application of hypofractionation treatment in breast radiation therapy, in addition to reducing the treatment time, leads to a decrease in the average dose of organs and dosimetric factors related to sensitive organs. In future research, it is possible to improve treatment methods and reduce skin complications in these patients by conducting more studies.

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