

Dosimetric comparison of acute skin complications following conventional and hypofractionated radiotherapy in breast cancer patients

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide, causing death in women and accounting for 11% of all cancers⁽¹⁾. Each year, more than 1.1 million people are diagnosed with breast cancer, and more than 410,000 die from it^(2,3). The choice of treatment depends on tumor characteristics⁽⁴⁾. Radiation therapy (RT) is one of the top three most effective cancer treatments, and it is estimated that more than half of patients receive RT during treatment. Surgery is the first line of treatment for many types of tumors and has good outcomes for non-metastatic tumors⁽⁵⁾. However, RT is a viable alternative to surgery for long-term control of many tumors, such as head and neck, breast, lung, cervical, bladder, prostate, and skin cancer⁽⁶⁾. In treatment planning, the priority is to apply the maximum dose to the tumor according to the dose limitations of the surrounding organs at risk (OAR); however, the unavoidable doses of radiation therapy reach non-target organs and tissues⁽⁷⁾.

Two commonly used RT techniques for breast cancer treatment are conventional fractionation

ABSTRACT

Background: Radiation therapy is one of the most important methods of breast cancer treatment that can cause complications that affect the patient's quality of life. The aim of this study was a dosimetric comparison of skin complications after hypofractionated radiotherapy (HFRT) and conventional fractionated radiotherapy (CFRT) in breast cancer patients. **Materials and Methods:** In this cross-sectional study between November 2021 and July 2022, 55 patients were reviewed. Thirty-six patients received CFRT (50Gy in 25 fractions), and 19 patients received HFRT (42.5Gy in 16 fractions). Skin complications during treatment and 40 days after radiotherapy were evaluated and compared for these two procedures. **Results:** The incidence of grade 1, 2, and 3 skin complications up to 40 days after CFRT was 100%, 88.8%, and 22.2%, respectively; also, in HFRT, the incidence of grade 1, 2, and 3 skin complications was 89.4%, 36.8%, and zero, respectively. The results show that the incidence of skin complications is significantly higher with the CFRT than with the HFRT ($P<0.05$). **Conclusion:** In this clinical study, both in terms of complications and dosimetry, it was shown that patients undergoing radiation therapy with the hypofractionation technique had fewer skin complications compared to those treated with the conventional technique.

radiation therapy (CFRT) and hypofractionation radiation therapy (HFRT). CFRT involves delivering radiation in small doses over a longer period, typically 5-7 weeks, while HFRT involves delivering larger doses over a shorter period, typically 3-4 weeks^(8, 9). Several studies have compared the efficacy of CFRT and HFRT in breast cancer treatment. One study found that HFRT was as effective as CFRT in terms of local control, disease-free survival and overall survival, and resulted in fewer side effects, such as skin reactions and fatigue⁽¹⁰⁾. However, some studies have reported conflicting results, with no significant difference in treatment efficacy or side effects between the two techniques⁽¹¹⁾. In conclusion, both CFRT and HFRT are effective radiation therapy techniques for breast cancer treatment, and the choice of technique should be based on individual patient factors. While HFRT may result in fewer side effects, it may not be appropriate for all patients. Therefore, further research is needed to determine the optimal radiation therapy technique for individual breast cancer patients⁽¹²⁾.

Skin reactions, pain in the breast or chest wall, breast edema, changes in breast size, shape, and

color, nipple sensitivity, and effects on the heart, lungs, shoulder, and arm are among the observed complications in breast cancer radiation therapy (13). These complications have a direct impact on the patient's psychological status, quality of life, and immune system and can affect the course of the disease, treatment outcomes, length of hospital stay, and even the patient's lifespan (14, 15). Research indicates that a brief HFRT regimen may be appropriate and beneficial for patients, particularly those traveling from remote regions to radiation therapy facilities, potentially leading to an increased patient influx within the treatment department (9, 16).

The analysis and comparison of conventional and hypofractionation radiation therapy techniques is very important in the treatment of breast cancer. The difference in the radiation therapy delivery method between these two techniques can have an effect on side effects and treatment results. The aim of this study is to investigate and compare the dosimetry and severity of skin complications using two different radiation therapy techniques for breast cancer. Considering that breast cancer treatment is associated with long-term side effects, it is very important to investigate and compare skin complications, which is one of the main side effects of breast cancer radiation therapy. This study is one of the first to use dose-volume histogram (DVH) data to compare skin doses in two groups of breast cancer patients. This is an important innovation in the field of breast cancer radiotherapy and could lead to improved decision-making in the selection of radiotherapy type for breast cancer patients.

MATERIALS AND METHODS

In this cross-sectional study, 55 female breast cancer patients (36 in the conventional group and 19 in the hypofractionated group) who underwent CFRT or HFRT breast cancer treatment from November 2020 to July 2021 were analyzed. The study comprised patients who met certain criteria for inclusion and exclusion, and who had provided informed consent by completing a consent form. The study was conducted at the Radiation Therapy Center in Yazd on patients whose breasts had been totally or partially irradiated. Patients who had pre-existing skin lesions, shingles, eczema, or previous exposure to radiation were excluded from the study. All participant demographics were collected and recorded, including age, breast area treated, history of underlying disease, family history of cancer, body mass index (BMI), chemotherapy regimen, and type of treatment. In this study, variable mastectomy was not included in the demographic factors due to the fact that one of the patients had undergone mastectomy.

Radiotherapy protocol and treatment planning

In the CFRT method for breast cancer, a total dose of 5000 cGy was prescribed in 25 fractions along, with a boost dose of 1000 cGy in 5 fractions. In the HFRT method, a total dose of 4250 cGy was prescribed in 16 fractions, with a boost dose of 1000 cGy in 5 fractions.

All patients underwent 3D-CRT using an Elekta linear accelerator (Model: Compact, China). Treatment plans were based on computed tomography (CT) scans (Somatom, Siemens, Germany) acquired at 5 mm intervals, and treatment was planned using the Prowess Panther Treatment Planning System (Prowess Inc., Chico, CA) (figure 1). Initially, the oncologist specified the primary gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), organs at risk (OARs), and planning volume of organs at risk (PRV) with appropriate margins according to treatment planning protocols. Physical dose values to the skin, such as mean, minimum, and maximum dose, were recorded as a dose-volume histogram and extracted.

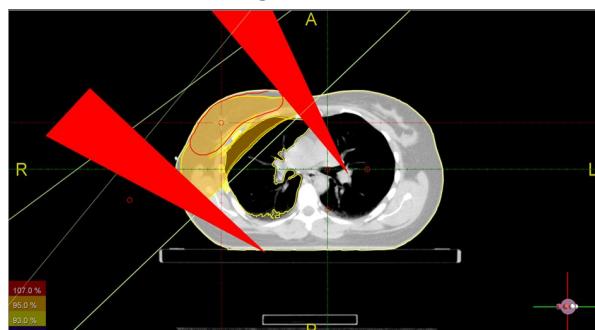


Figure 1. An example of breast contouring in the treatment planning for breast cancer patients.

Follow-up and evaluation of complications

For each patient in both conventional and hypofractionated radiation therapy methods, skin toxicity was evaluated by a specialized physician at the radiotherapy center on a weekly basis during radiation therapy and 40 days after radiation therapy. Skin toxicities were assessed based on the Radiation Therapy Oncology Group (RTOG) (17) common toxicity criteria (table 1). In compliance with all ethical guidelines, informed consent was obtained from patients and all patient data were managed confidentially and anonymously to protect patient privacy.

Table 1. Skin complications based on RTOG (19).

Grade	Description
0	No skin changes
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation mostly confined to skin folds and creases
3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicate
5	Death

Statistical analysis

In this study, descriptive statistics including mean, standard deviation, frequency, and frequency percentage were utilized to provide a comprehensive description of the data. Additionally, a chi-square test with a significance level of $\alpha = 0.05$ was employed to validate the existence of a significant difference between the two groups. All statistical analyses were conducted using SPSS software version 24 (SPSS, Chicago, IL), with a significance level set at 5%.

RESULTS

The frequencies of the qualitative demographic variables are listed in table 2. The study involved 55 breast cancer patients undergoing radiation therapy, with an average age of 52.05 ± 12.19 years. The oldest participant in this study was a 78-year-old woman, while the youngest was a 29-year-old woman. Of the patients, 36 (65.5%) received conventional treatment, and 19 (34.5%) received hypofractionation. Among the patients, 34 (61.8%) had cancer in the right breast, 40 (72.7%) had a history of chemotherapy, 41 (74.5%) had no history of underlying disease, and 19 (34.5%) had a family history of cancer. The highest number of patients had a body mass index between 25 and 29.9.

Table 2. Frequency distribution of demographic variables in breast cancer patients undergoing radiation therapy.

Characteristics	Variable levels	Frequency
Age	25-35	6(10.9%)
	36-50	19(34.5%)
	51-70	27(49.1%)
	0>71	3(5.5%)
Breast	Left	21(38.2%)
	Right	34(61.8%)
History of underlying disease	Yes	14(25.5%)
	No	41(74.5%)
History of cancer in the family	Yes	19(34.5%)
	No	36(65.5%)
BMI	>18.5	1(1.8%)
	18.5-24.9	16(29.1%)
	25-29.9	25(45.5%)
	30-39.9	13(23.6%)
Chemotherapy	Yes	40(72.7%)
	No	15(27.3%)
Treatment	CRT	36(65.5%)
	HFRT	19(34.5%)
T stage	T ₀	3
	T ₁	7
	T ₂	17
	T ₃	21
	T ₄	7
N stage	N ₀	10
	N ₁	23
	N ₂	15
	N ₃	7

BMI: Body mass index; HFRT: Hypofractionated radiotherapy; CFRT: Conventional fractionated radiotherapy

Skin complications

Table 3 shows the frequencies and percentages of skin complications in breast cancer patients treated

with two methods, CFRT and HFRT, at weekly intervals during and after treatment for 40 days, as well as the statistical differences between the two methods. As shown, skin complications occurred in both radiation therapy methods starting from the second week, but no grade 4 skin complications were observed.

Regarding CFRT, the highest incidence of grade 1 skin complications occurred during the third and fourth weeks of treatment (68.4% and 61.1%, respectively). The highest incidence of grade 2 skin complications occurred during weeks 5 and 6 (63.9% and 66.7%, respectively), and the highest incidence of grade 3 skin complications occurred during week 6 (22.2%). After 40 days of radiation therapy, the highest incidence of skin complications was observed for grade 1 (36.1%), compared to other grades.

During HFRT, the highest incidence of grade 1 skin complications occurred during the third week of treatment (68.4%). The highest incidence of grade 2 skin complications occurred during week 4 (36.4%). No grade 3 or higher skin complications were observed during or 40 days after radiation therapy. After 40 days of radiation therapy, the highest incidence of skin complications was observed for grade 1 (36.8%), compared to other grades.

Overall, the incidence of skin complications up to 40 days after CFRT for grades 1, 2, and 3 was 100%, 88.8%, and 2.22%, respectively. For HFRT, the corresponding figures were 4.89%, 8.36%, and 0%. The results showed that the incidence of skin complications with grades 1, 2, and 3 following CFRT was significantly higher than that following HFRT (with significant levels of 0.02, 0.01, and 0.028, respectively).

Maximum, minimum and average dose

Based on Table 3, due to the high incidence of skin complications in Grade 1 and the low incidence of skin complications in Grade 3, our study team decided to compare patients with and without skin complications in Grade 2 based on the maximum, minimum, and average doses. Table 4 presents the average values of maximum dose, minimum dose, and average skin dose in both conventional and hypofractionation techniques for patients with and without Grade 2 skin complications.

In both treatment techniques, all three parameters mentioned were significantly higher in patients with skin complications compared to those without skin complications (p -value ≤ 0.05 for all three parameters). Moreover, in comparing the two radiation therapy techniques, although all three parameters were higher for conventional radiation therapy than hypofractionation, the statistical differences were only significant for the average dose in patients with skin complications and the maximum and minimum doses in patients without skin complications (with a p -value ≤ 0.05 for all three parameters).

Table 3. The frequency of skin complications in CFRT and HFRT treatment, as well as the statistical differences in the incidence of grade 2 skin complications between the two radiation therapy methods at different times from the beginning of radiation therapy to 40 days after treatment.

Frequency - HFRT					Frequency - CFRT				P-value
Time(Week)	Grade				Grade				P-value
	0	1	2	3	0	1	2	3	
1	19(%100)	0(%0)	0(%0)	0(%0)	36(%100)	0(%0)	0(%0)	0(%0)	-
2	18(%94.7)	1(%5.3)	0(%0)	0(%0)	31(%86.1)	5(%13.9)	0(%0)	0(%0)	-
3	6(%31.6)	13(%68.4)	0(%0)	0(%0)	2(%5.6)	34(%94.4)	0(%0)	0(%0)	-
4	2(%10.5)	10(%52.6)	7(%36.8)	0(%0)	0(%0)	22(%61.1)	14(%38.9)	0(%0)	0.02
5	0(%0)	0(%0)	0(%0)	0(%0)	0(%0)	9(%25)	23(%63.9)	4(%11.1)	0.04
6	0(%0)	0(%0)	0(%0)	0(%0)	0(%0)	4(%11.1)	24(%66.7)	8(%22.2)	0.18
Forty days*	11(%57.9)	7(%36.8)	1(%5.3)	0(%0)	19(%52.8)	13(%36.1)	3(%8.3)	1(%2.8)	0.02
Total	19(%100)	17(%89.4)	7(%36.8)	0(%0)	36(%100)	36(%100)	32(%88.8)	8(%22.2)	0.01

*Forty days after treatment. HFRT: Hypofractionated radiotherapy; CFRT: Conventional fractionated radiotherapy.

Table 4. Comparison of average maximum, minimum and average dose(cGy) in patients with HFRT and CFRT.

Quantity	Variable	CFRT	HFRT	P-Value
Average dose (cGy) (SD)	with complications	3216.02 (1733.04)	1612.35 (753.21)	0.02
	Without complications	1218.95 (883.01)	1160.00 (650.00)	0.68
Maximum dose (cGy) (SD)	with complications	5440.62 (2981.41)	3277.20 (1909.69)	0.11
	Without complications	2674.01 (1150.72)	2438.15 (1446.89)	0.04
Minimum dose (cGy) (SD)	with complications	485.50 (281.90)	465.05 (221.45)	0.21
	Without complications	157.18 (66.20)	120.01 (57.71)	0.06

SD: standard deviation; cGy: centigray; HFRT: Hypofractionated radiotherapy; CFRT: Conventional fractionated radiotherapy.

DISCUSSION

Radiation therapy is a very efficient approach for treating breast cancer. However, one of the problems related to this method is the skin complications that may occur in patients (18, 19). These side effects can include burns, itching, inflammation, and pigmentary changes (13). These complications can directly and indirectly affect all aspects of the patient's life and can lead to psychological changes, increased physical side effects, and reduced quality of life (14, 15). Therefore, it is crucial to manage and prevent skin complications associated with radiotherapy in breast cancer in order to ensure proper improvement in the mental and physical condition of patients and maintain their quality of life. Due to the importance of this topic, in this study, two techniques, CFRT and HFRT, were examined and compared to investigate dosimetric skin complications.

CFRT, which is commonly used as the standard approach, involves dividing radiation therapy doses into daily fractions and using lower doses (20). On the other hand, HFRT delivers larger doses over a shorter period of time. CFRT has limitations such as longer treatment duration, increased treatment costs due to a higher number of sessions, and extended patient waiting times (11, 12). To address these limitations, HFRT has been proposed as an alternative solution. Based on the conducted studies,

the superiority of the hypofractionation technique in breast radiotherapy has been observed in terms of reducing the occurrence of skin effects (20).

A study was conducted in China with the aim of comparing CFRT and HFRT after mastectomy in 820 breast cancer patients. At the end of the study, it was found that HFRT after mastectomy was less toxic and had similar toxicity to CFRT in breast cancer patients. Additionally, HFRT can provide a more convenient treatment and allow providers to treat more patients. In a median follow-up of 58 months, 7% of patients (60 patients) had local recurrence (11). A study conducted in 2017 by Zhao *et al.* examined the long-term outcomes of HFRT and CFRT following breast conserving surgery in patients with early-stage breast cancer. The findings of the study revealed that the incidence of adverse effects in HFRT was lower compared to CFRT over a ten-year period (21). In the year 2020, a systematic review and meta-analysis were carried out to compare the efficacy and toxicity of HFRT and CFRT in post-mastectomy breast cancer patients. The findings of the study indicated no significant difference between HFRT and CFRT in terms of efficacy or toxicity for post-mastectomy breast cancer (22). In Hashemi *et al.*'s trial, early skin toxicity, local recurrence within ten years, and cosmetic result did not show any differences between HFRT (42.5 Gy in 16 fractions over 22 days) and CFRT (50 Gy in 25 fractions over 35 days) (23). A meta-analysis encompassing 14 randomized controlled trials (RCTs) revealed no statistically significant distinctions between HFRT and CFRT in terms of local recurrence, recurrence-free survival, overall survival, cosmetic results, or any unfavorable consequences (24). In a separate study conducted to compare acute radiation-induced skin toxicity between HFRT and CFRT in whole-breast irradiation, it was observed that HFRT resulted in lower rates and severity of acute radiation-induced skin toxicity (25). In this study, it was shown (table 3) that breast cancer patients who underwent HFRT had less skin toxicity compared to those who received CFRT.

The study conducted by Maiti *et al.* between 2014 and 2017 aimed to compare dosimetric and clinical outcomes in the treatment of breast cancer with

radiotherapy between two groups: HFRT and CFRT. The results indicated that in the conventional group, both the average and maximum dose were significantly higher than in the HFRT group⁽²⁶⁾.

According to the dose comparison table (table 4), it was observed that in HFRT, the skin toxicity grade 2 was lower than CFRT in terms of maximum dose, minimum dose, and mean dose. Additionally, in both treatment techniques, all three mentioned quantities were significantly higher in patients with toxicity than those without toxicity ($p\text{-value} \geq 0.05$ for all three quantities).

There are several limitations to this study. These include the relatively short duration of the study and the lack of long-term follow-up of patients after treatment, restrictions on skin testing and evaluation of skin complications due to safety and health concerns during the COVID-19 pandemic, and limitations in following up with patients after treatment due to restrictions on movement and face-to-face communication. The authors of this study suggest that with further research, treatment methods can be improved and skin side effects can be reduced in these patients. Furthermore, by using radiobiological models and logistic regression analysis with existing programs and machine learning, these studies can be conducted more accurately by calculating the probability of normal tissue complications probability (NTCP) and tumor control probability (TCP).

CONCLUSION

According to the Radiation Oncology Organization, many studies have assessed the incidence of acute skin effects, but few studies have assessed this complication dosimetrically; therefore, in this study, these two methods were comprehensively investigated for the first time. This clinical study showed that patients who underwent HFRT experienced fewer skin side effects compared to those who underwent CFRT. Additionally, the HFRT regimen resulted in a reduction in dose volume factors compared to the CFRT regimen, and because of the shorter treatment course, it can be used as an alternative method in breast cancer radiotherapy.

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Conflicts of interest: The research was carried out without any financial or commercial ties that may be seen as having a conflict of interest, the authors

disclose.

Ethical considerations: Conscious consent was obtained from all individuals engaged in the study. This prospective study was approved by the National Ethics Committee at the Shahid Sadoughi University of Medical Science, Yazd, Iran (IR.SSU.MEDICINE.REC.1400.313). Informed consent was obtained from the included patients. The Research Ethics Committee of School of Medicine-Shahid Sadoughi University of Medical Sciences evaluated this study and approved it on 2021-12-08 with the code IR.SSU.MEDICINE.REC.1400.313.

Authors' contribution: K.S. and R.A.; gathered information, organized it, and composed the text. F.M.; made a statistical analysis contribution. The final draft of the work was authored and revised by M.B. In addition to helping to write and revise the report, N.H. took part in the study's design. Each author read and approved the final text in addition to helping to interpret the results.

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