Journal of Pakistan Association of Dermatologists.2023;**33(2)**:629-636.

Original Article

The frequency of acute radiodermatitis and associated risk factors among patients with breast cancer treated by radiotherapy

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Abstract

Background Acute radiodermatitis is a common side effect during and after radiotherapy course in breast cancer patients treated by radiotherapy. This study explores the frequency of acute radiodermatitis and records the predictive factors for acute radiodermatitis.

Methods An observational descriptive study performed at Baghdad, Iraq from August 2020 to September 2021. Seventy females scheduled for radiotherapy sessions enrolled in this study. sociodemographic data were recorded and Skin examination before radiotherapy and weekly till the end of the radiotherapy sessions was done to record the frequency, risk factors, clinical picture and grades of acute radiodermatitis based on The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE 4).

Results Fifty four (77.1%) female developed acute radiodermatitis during their radiotherapy sessions: 38 (70.4%) was Grade I, 12 (22.2%) Grade II and 4 (7.4%) Grade III. Statistically significant more severe radiodermatitis Grade among conventional dose group (54.5%) compared to (23.3%) in hypofractionation group (P=0.043). Acute radiodermatitis rate and grade was statistically significant high in patient using bolus during radiotherapy than in those did not use it (P=0.048, P=0.017) respectively. The Grade of radiodermatitis was statistically significant more severe in breast conservative surgery patients (P=0.046). Skin type I & II patients were more liable to radidermatitis compared with those with skin type III & IV (P=0.035). No significant associations between radiodermatitis and different patients' and tumor characteristics.

Conclusion We found that conventional dose, addition of bolus, breast conservative surgery and patients skin type I&II were all significant factors that enhance skin reaction.

Key words
Breast cancer; Radiotherapy; Radiodermatitis.

Introduction

Female breast cancer is the most commonly diagnosed cancer (11.7% of total cases).[1] It ranks as the fifth most common cause of cancer mortality in the world, with 685,000 deaths. It is the most common type of malignancy among women, accounting for 1 in 4 new cases and 1in 6 cancer-related deaths.[1] In some females with significant risks of local recurrence following mastectomy, radiotherapy to the chest wall is recommended.[2]

Chemotherapy or hormone therapy can be considered if poor prognostic factors present.[2] In

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breast cancer the standard radiation therapy schedule treatment delivers 1.8 to 2.0 Gy per day for 25 to 28 days for a total dose of 45 to 50.4 Gy followed by a 5 to 8 fraction boost (10 to 16 Gy) for a total dose of 60 to 66 Gy delivered for 6 to 7.5 weeks. Hypofractionation, which implicates a delivery of a larger dose per fraction for a smaller number of fractions for a biologically equivalent dose has become increasingly popular.[3] However, when the dose per fraction is increased, the total dose delivered is then decreased.[4]

Following surgery, cancer cells that may be found in the breast or chest wall are killed with radiotherapy. Unfortunately, the treated area's normal cells are also impacted. Compared to cancer cells, these healthy tissue cells have a much more ability to recover from radiation exposure. The majority of normal cells can recover throughout the time between each daily therapy. Despite this improvement, adverse effects can still happen and are often expected during treatment. Some side effects manifest "early" (i.e., during therapy and for up to six months after treatment is completed), whereas others may appear "late" (several months to years after completing treatment).[3]

A significant detrimental consequence that results from radiation exposure during cancer treatment is radiodermatitis.[5] Given that the skin is an element of the target volume for malignancies of the breast, perineum, and head and neck region, it is particularly troublesome in these cases.[6] Due to the intended radiation target's close proximity to the skin and the inability to protect the skin from greater doses of radiation, these malignancies have a higher prevalence of radiodermatitis.[7]

During their courses of radiation therapy for breast cancer, more than 90% of women will develop some skin changes.[8]

The severity of radiodermatitis can vary depending on patient- and treatment-related risk factors.[9]

Radiodermatitis can range from acute erythema to chronic skin fibrosis, and is frequently classified into acute and chronic.[10] generally, acute radiodermatitis starts 10 to 14 days after radiotherapy beginning. It may include minimal erythema, swelling, dryness, burning, itching, soreness, and hyperpigmentation.[11]

For proper management and monitoring of radiodermatitis in clinical practice, accurate assessment and categorization are crucial. A gold standard has not yet been established, despite the fact that a lot of assessment instruments have been created to describe the range of radiodermatitis.[12]

There are limited recommendations on how to prevent and treat radiation dermatitis using dermatologic skin-care methods and products. The majority of therapies used to minimize radiation-induced skin reactions are based on research with insufficient power. As a result, therapeutic methods used by different practitioners are variable, confusing patients and giving them inconsistent information.[13]

The study aim is to evaluate the frequency of acute radiodermatitis and record the predictive factors for acute radiodermatitis in females with breast cancer treated by radiotherapy.

Methods

This is an observational, descriptive study conducted at Baghdad Radiotherapy and Nuclear Medicine Center, Medical City, Baghdad, Iraq from August 2020 to September 2021, 70 female patients were involved in this study.

All patients whom diagnosed with breast cancer as proved by clinical and histopathological

means and treated by adjuvant Radiotherapy were enrolled in the current work. The breast cancer was primary in all involved patients. There were no exclusion criteria or age restrictions in this study apart from the exclusion of male breast cancer patients.

After each patient's formal consent was obtained and the study's objectives were fully explained, the clinical history was obtained. This included information about each patient's age, smoking and alcohol status, past medical and surgical history, history of chemotherapy prior to radiotherapy, and use of hormonal therapy.

Clinical data were obtained from patient medical files kept at the radiation center regarding tumor characteristics (tumor histology and stage), type of breast surgery, therapeutic regimen, and body mass index (BMI).The patients were treated with three-dimensional conformal radiotherapy (3DCRT) administered five days in the week (Sunday through Thursday) for 3 to 5 weeks using conventional or hypofractionation scheme.

Ethical approval was obtained from Scientific Council of Dermatology and Venereology of Iraqi Board for Medical Specializations.

Dermatological examination of skin area received radiotherapy were done before the beginning of radiotherapy and at weekly interval throughout the radiotherapy sessions in cooperation with oncologist to assess the frequency, risk factors and clinical picture of acute radiodermatitis and graded using The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Color photographs for each patient were performed at each visit using Samsung Galaxy Note 8, 12-megapixel rear camera with fixed illumination and distance.

Using the available statistical tool SPSS-27, data analysis was done (Statistical Packages for Social Sciences- version 27). Simple measure of frequency, percentage, means, standard deviation, and range were used to present the data (minimum-maximum values).

Whenever applicable, Yate's adjustment or the Fisher Exact test was applied to the Pearson Chi-square test (2-test) to determine the significance of the differences between distinct percentages (qualitative data). When the P value was 0.05 or less, statistical significance was taken into account.

Results

Seventy breast cancer females were enrolled in this study during their radiotherapy sessions. Their ages ranged (from 32 to 82) years old with a mean 52.1±9.1, their BMI ranged (from 20.0 to 35.4) with a mean of 29.0±3.1. Eleven (15.7%) patients had diabetes mellitus. Only four patients were smoker. Three (4.3%) patients were of skin type 1, 45 (64.3%) patients were of skin type 2, 20 (28.6%) patients were of skin type 3 and the rest 2 (2.9%) patients were of skin type 4.

Fifty (71.4%) patients were undergoing mastectomy while 20 (28.6%) patients were undergoing breast conservative surgery. Furthermore, 58 (82.9%) patients treated with hypofractionation dose of radiotherapy, while only 12 (17.1%) patients treated with conventional dose. Bolus used in 23 (32.9%) patients. All the patients received chemotherapy prior to radiotherapy sessions but only four of them used concurrent hormonal therapy.

Fifty four (77.1%) patients developed acute radiodermatitis during their radiotherapy sessions, 38 (70.4%) was Grade I, 12 (22.2%) was Grade II and 4 (7.4%) was Grade III. No

one develop Grade IV acute radiodermatitis. Thirty-nine (72.2%) patients developed the acute radiodermatitis in the third week of radiotherapy course.

Acute radiodermatitis was more common in patients receiving conventional dose of radiotherapy 91.7 % (11 from 12 patients) in comparison with 74.1% (43 from 58 patients) in those whom received hypofractionation dose **(Table 1)**.

There was also statically significant more severe acute radiodermatitis Grade (Grade II and III) among conventional dose group (54.5%) while the percentage decrease to (23.3%) in the hypofractionation group (P=0.043) **(Table 2)**.

The acute radiodermatitis rate was statistically significant high in patient using bolus during radiotherapy course than in those did not use it (P=0.048) **(Table 1)**. Furthermore the Grade II and III radiodermatitis was also statistically significantly more in patients using bolus during radiotherapy sessions (P=0.017) as shown in **(Table 2)**.

The acute radiodermatitis was more common in patients undergoing breast conservative surgery (90%) compared to those whom undergoing mastectomy (72%) **(Table 1)**.

In addition, the Grade of radiodermatitis was statistically significant more severe (Grade II and III) in breast conservative surgery patients (P=0.046) **(Table 2)**.

When compared to patients with skin types III and IV, those with skin types I and II were more likely to develop acute radidermatitis (P=0.035) as it is demonstrated in **(Table 3,4)**.

There were no significant associations between acute radiodermatitis and different patients' characteristics (age, BMI, diabetes mellitus) (P=0.938, 0.247, and 0.704 respectively). Both tumor type and stage do not affect acute radiodermatitis (p=0.343, 0.270 respectively).

Table 1 Acute radiodermatitis vs. treatment modalities.

		Radiodermatitis				*P value*
		Yes		*No*		
		No	*%*	*No*	*%*	
Dose of radiotherapy	Hypofractination (4005-256/15-16)	43	74.1	15	25.9	0.188
	Conventional (5000/25)	11	91.7	1	8.3	
Bolus use	Yes	15	65.2	8	34.8	0.048*
	No	39	83.0	8	17.0	
Surgery	Breast Conservative Surgery	18	90.0	2	10.0	0.105
	Mastectomy	36	72.0	14	28.0	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table 2 Acute radiodermatitis vs. treatment modalities.

		Radiodermatitis grade				*P value*
		Grade I		*Grade II-III*		
		No	*%*	*No*	*%*	
Dose of radiotherapy	Hypofractination (4005-256/15-16)	33	76.7	10	23.3	0.043*
	Conventional (5000/25)	5	45.5	6	54.5	
Bolus use	Yes	8	50.0	8	50.0	0.017*
	No	30	78.9	8	21.1	
Surgery	Breast Conservative Surgery	10	55.6	8	44.4	0.046*
	Mastectomy	28	77.8	8	22.2	

* Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table 3 Skin type vs. acute radiodermatitis frequency.

		Radiodermatitis				*P value*
		Yes		*No*		
		No	*%*	*No*	*%*	
Skin type	I	3	100	-	-	0.140
	II	37	82.2	8	17.8	
	III	12	60.0	8	40.0	
	IV	2	100	-	-	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.
- Comparing Skin type I&II Vs. III&IV; P=0.035 (Significant).

Table 4 Skin type vs. acute radiodermatitis Grade.

		Radiodermatitis grade				*P value*
		Grade I		*Grade II-III*		
		No	*%*	*No*	*%*	
Skin type	I	2	66.7	1	33.3	0.171
	II	27	73.0	10	27.0	
	III	9	75.0	3	25.0	
	IV	-	-	2	100	

* Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.
- Comparing Skin type I&II Vs. III&IV; P=0.281 (Not significant).

Discussion

Breast malignancy is the most prevalent malignancy in women in Iraq and globally.[3]

It has become a major threat to female health in Iraq and world, where it is now the second greatest cause of death for women after cardiovascular diseases. Since 1986, it has become the most common malignancy among all Iraqi population.[14]

The overall percentage of radiodermatitis in this study was (77.1%), which was comparable to the incidence of acute skin reaction in many other published studies. For example, Hussein E. found that (81.6%) of women receiving radiation for breast cancer will experience some skin changes during their course of treatment[3] while *Costa et al.* study revealed that (81.1%) of the patients with breast cancer developed acute radiodermatitis.[15]

Most of the patients in the current study developed Grade 1 skin reaction (70.4%) while no one developed Grade IV; this result goes with Hussein E work in which the percentage of Grade 1 acute radiodermatits was (81.7%) and also no patients develop Grade IV,[3] the explanation behind that is use of hypofractionation dose in most of the patients and the nature of skin type of Iraqi patients.

In the present work (72.2%) of the patients developed acute radiodermatitis in the third week of radiotherapy course, this consistent with the most of recorded data from the literature review.

"Skin changes associated with radiation therapy often appear 1-4 weeks after radiation beginning and last the entire course of radiation therapy."[16]

Several clinical characteristics among breast cancer patients were evaluated in this research to estimate their impact on skin reaction severity and compare the results with previous literatures in the neighboring country and the world.

The present study raised that the dose of the radiotherapy was not only affect the occurrence of acute skin reaction in enrolled patients, but also affect the severity of the skin reactions, the incidence of acute dermatitis decreased

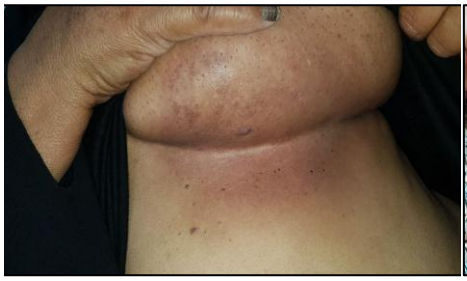

Figure 1 Forty three year old female with grade I acute radiodermatitis

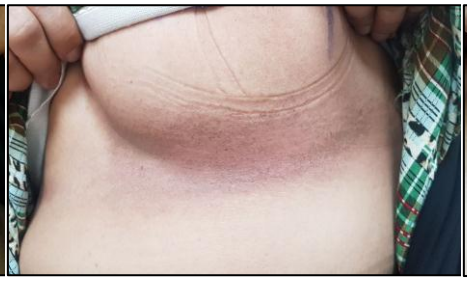

Figure 2 Fifty four year old female with grade I acute radiodermatitis.

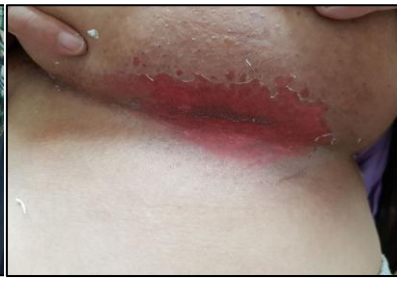

Figure 3 Fifty seven year old female with grade II acute radiodermatitis.

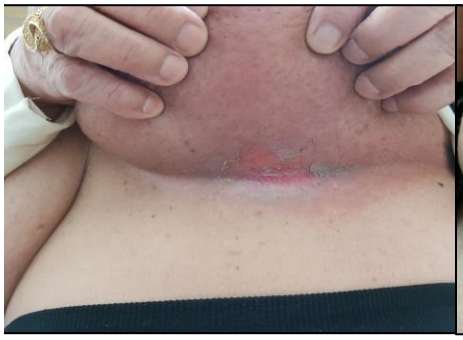

Figure 4 Sixty year old female with grade II acute radiodermatitis.

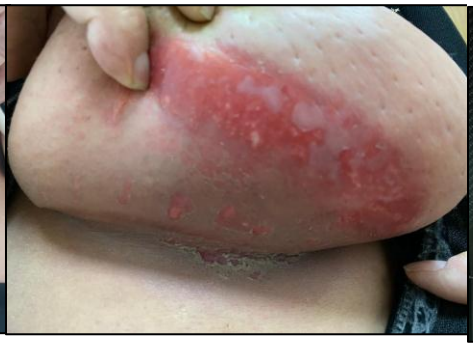

Figure 5 Fifty eight year old female with grade III acute radiodermatitis.

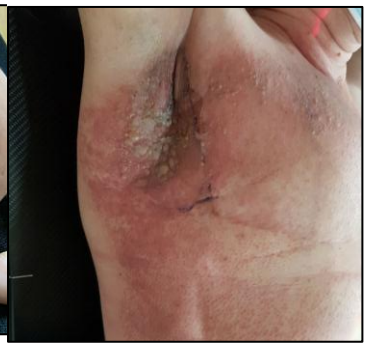

Figure 6 Sixty two year old female with grade III acute radiodermatitis.

significantly by using Hypofractionated dose compared with Conventional dose (74.1% vs. 91.7%, respectively; p =0188), especially that of >Grade 1 dermatitis (23.3% vs. 54.5%, respectively; P=0.043) , these results followed the same line with Shaitelman *et al.*[17] although the p-value in this study was not significant regarding the percentage of radiodermatitis in hypofractinated dose compared with conventional dose it's significant regarding the grade of acute radiodermatitis, because only 12 patients out of 70 (17.1%) treated by conventional regime, all developed acute radiodermatitis except one, this due to small sample size. So for that reason no conclusion can be established for this point.

This work revealed that the acute radiodermatitis rate was statistically significant high in patient using bolus during radiotherapy sessions than in those did not use it (P=0.048). Furthermore the grade 2 and 3 acute radiodermatitis was also statistically significantly more in patients using bolus during radiotherapy sessions (P=0.017), due to increased tissue volume irradiated, Behroosian *et al.* mention that the use of bolus was a predictive factors with a strong correlation with radiodermatitis,[18] which is compatible with the results in this study.

In the present work, the type of surgery is not a statistically significant predictive factor for acute radiodermatitis, these result not so far from Behroosian *et al.* and Gonulal *et al;*[18.19] However this study showed that the radiodermatitis is more common in patients undergoing breast conservative surgery (90%) compared to those whom undergoing mastectomy (72%) and the grade of radiodermatitis was statistically significant more severe (grade 2 and 3) in breast conservative surgery patients (P=0.046), this may be attributed to improper cleansing and skin care to inframamary folds in BCS patients and

unsuitable clothes during radiotherapy course which may lead to friction and more severe radiodermatitis.

In this study, females with skin types I and II were more likely to develop radidermatitis than those with skin types III and IV (P=0.035), this results correspond with the result of *Yamazaki et al*.[20] this is because the melanin act as umbrella that protect from radiation.

Increase BMI did not affect the frequency of acute radiodermatitis as illustrated in the present work, These results incompatible with *Gonulal et al;*[19] this could be explain by the high percentage of overweight and obese patients (91.4%).

This study revealed no association between tumor characteristic (type and stage), age, past medical history of the patients (diabetes mellitus) and occurance of acute radiodermatiitis, these results similar to Gonulal *et al*. results.[19]

Smoking status and using of hormonal drugs were not analyzed in this study because the number of patients with a history of smoking or hormonal drugs used was low.

In conclusion acute radiodermatitis is a common cutaneous side effects of radiotherapy especially grade I followed by grade II. It was found that conventional dose, addition of bolus, breast conservative surgery and patients skin type I&II were all significant elements that encourage skin reaction severity among breast cancer patients. Patient's age, BMI, past medical history of D.M and tumor characteristic were not significant factors in developing acute radiodermatitis.

References

1. Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;**0**:1–41.
2. Williams NS, Bulstrode CJK, O'connell PR. The breast. In: Williams NS, Bulstrode CJK, O'connell PR. Bailey and Love's Short Practice of Surgery. 26th ed. Florida: CRC Press; 2013. 53:798-819.
3. Hussein EA, Al-Rawaq KJ. Assessment of early side effects of radiotherapy in breast cancer patients. *J Fac Med Bagdad*. 2016; **58(3)**: 202-7.
4. Veness MJ, Richards SW. Radiotherapy. In: Bolognia JL, Schaffer JV, Cerroni L. Dermatology. 4th ed. Philadelphia: Elsevier; 2018.139:2393-403.
5. Chan RJ, Webster J, Chung B, *et al*. Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2014;**14**:53.
6. DeSantis CE, Lin CC, Mariotto AB,*et al* . Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin*. 2014;**64(4)**:252–71.
7. Radvansky LJ, Pace MB, Siddiqui A. Prevention and management of radiation-induced dermatitis, mucositis, and xerostomia. *Am J Health Syst Pharm*. 2013; **70(12)**:1025–32.
8. Yavas C, Gultekin M. Toxicity Management for other Sites in Radiation Oncology. In: Ozyigit G, Selek U, Eds. Prevention and management of acute and late toxicities in radiation oncology. *Springer*. 2020;**7**:267-322.
9. Barnett GC, West CM, Dunning AM, *et al*. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nat Rev Cancer*. 2009;**9**:134–42.
10. Singh M, Alavi A, Wong R, *et al*. Radiodermatitis: A Review of Our Current Understanding. *Am J Clin Dermatol*. 2016;**17**:277–92.
11. Kole AJ, Kole L, Moran MS. Acute radiation dermatitis in breast cancer patients: challenges and solutions. *Breast Cancer*. 2017;**9**:313–23.
12. Ryan JL. Ionizing radiation: the good, the bad, and the ugly. *J Invest Dermatol*. 2012; **132(3 pt 2)**:985–93.
13. Salvo N, Barnes E, van Draanen J, *et al*. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Curr Oncol*. 2010;**17(4)**:94–112.

14. Alwan NAS. Breast cancer: Demographic characteristics and clinico-pathological presentation of patients in Iraq. *East Mediterr Health J*. 2010;**16**:1159–64.
15. Costa CC, LyraJorge S, Nakamura R A, *et al*. Radiodermatitis: analysis of predictive factors in breast cancer patients. *Revista Brasileira de Cancerologia*. 2019;**65.1**:1-8.
16. McQuestion M. Evidence-based skin care management in radiation therapy. *Semin Oncol Nurs*. 2006;**22(3)**:163–73.
17. Shaitelman S F, Schlembach P J, Arzu I, *et al*. Acute and short-term toxic effects of conventionally fractionated vs. hypofractionated whole-breast irradiation: a randomized clinical trial. *JAMA Oncol.* 2015;**1.7**:931-41.
18. Behroozian T, Milton L, Li N, *et al*. Predictive factors associated with radiation dermatitis in breast cancer. *Cancer Treat Res Commun*. 2021:100403.
19. Gonulal M, Guzeloz Z. Assessment of Acute and Chronic Radiodermatitis of Female Patients with Breast Cancer: The Impact of Radiotherapy and Patient Related Factors. *J Turk Acad Dermatol*. 2021;**15(1)**:8.
20. Yamazaki H, Takenaka T, Aibe N, *et al*. Comparison of radiation dermatitis between hypofractionated and conventionally fractionated postoperative radiotherapy: objective, longitudinal assessment of skin color. *Scienti Rep*. 2018;**8(12306)**:1-8.