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Dermatological sequel of adjuvant breast cancer radiotherapy in Iraqi women

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SUMMARY

Adjuvant breast cancer radiotherapy raises the risk of skin toxicities. We aimed to identify and determined patients and treatment characteristics that may increase this risk to help individualize and health worker in radiation field to prevention and management of radiation-induced these toxicities. We enrolled 157 women with breast cancer who received adjuvant radiation treatment based upon age, employments, educational level, marital status, parity, menopause status, weight, height, BMI, grade, types of surgery, chemotherapy, radiation fractionation, total dose, site of radiation, energy of accelerator used, skin color types, duration of skin toxicities manifestation, side effect of radiation, smoking, diabetes, hypertension, and coronary heart diseases. Univariate logistic regression was used to compare each factor across the skin toxicities groups. Significant risk factors were analyzed in a multivariate analysis. Most of women enrolled in this study belong to the age above 45 years. The common BMI recorded was within normal limit as 37.2%, followed by overweight 32.7%. Mastectomy plus ALND was the common surgical procedure. The chest wall plus axillary area was the common site of RT. The 4050cG/15F was the common RT dose utilized. The most duration of the sequel of skin toxicities was at 2 weeks of RT. The dermatological manifestations recorded in 72.6% of women exposed to RT. All skin manifestations of toxicities mostly recorded. In univariate analysis, weight was being the fold-increase in Odds for every 10 Kg increase in weight (OR 0.676, p=0.008). Also, abnormal BMI, was more likely to increased risk of dermatitis (OR 0.609, p=0.0015). For those underwent MRM were more suffering from skin toxicities (OR 4.488, p=0.019). Regarding sites of RT, chest wall when exposed to RT was more liable to develop dermatitis (OR 0.322, p=0.01). In hypo-fractionated courses, toxicities was less likely to occur (OR 0.211, p=0.0015). In, multivariate analysis the higher risk of toxicities remained with increasing BMI (OR 1.09, p<0.000), and when the standard breast dose utilized (OR 0.05, p<0.000). The incidence of adjuvant RT-induced skin toxicities is common. Lower BMI, and weight, BCS, RT sites and hypo-fractionated courses were beneficial to decrease skin toxicities.

Key words: breast cancer, radiotherapy, skin toxicities, dermatitis, iraq

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INTRODUCTION

Breast cancer is first ranking list of malignancies in Iraq, and globally it is the most common cancer, and the second most common cause of cancer related death in women [1-6]. IC Registry of Ministry of Health/Environment at 2011 reported the incidence was 18.96% with morbidity rate reached to 11.53%, but these data raised to 25.65% and 21.9% in 2014; 33.5% and 22.3% in 2015 [6]. Regarding GLOBCAN 2018, the new cases of breast cancer was 2,088,849 (11.6%), with 626, 679 (6.6%) died cases overall all cancer sites [7]. Postoperative radiotherapy following breast cancer surgery whether post mastectomy or BCS for invasive breast cancer is widely utilized overall the world. After long-term follow-up in most large randomized trials, and meta-analysis studies showed decreased 10-year recurrence and 15-year breast cancer death with radiation therapy after breast surgery [5]. As a result, approximately all patients undergo radiation therapy for their non-invasive and invasive breast cancer. Here, the one of the most common side effects is the skin toxicities and complication. More than of 90% of patients develop dose-dependent skin reaction within the site of radiation that may cause mild erythema, dark pigmentation, itching, dry desquamation, moist desquamation, dermatitis, and, rarely, ulceration [8]. Different studies have shown acute skin reactions are related with the development of late skin toxicities that lead to poor cosmetic outcomes and decreased quality of life, may be including pain, impaired body image, and impaired functioning [9]. Our study seeks to well determine which patient and related factors and/or treatment factors are detrimental or protective against developing skin toxicities in breast cancer patients. Understanding these factors could help in the prevention and management of radiation-induced skin toxicities in patients undergoing adjuvant breast cancer treatment.

MATERIALS AND METHODS

Study design

A prospective and retrospective cross-sectional study for women with post RT skin manifestation was performed.

Setting

The medical files of 157 breast cancer women treated between 2015 and 2019 with histologically confirmed ductal carcinoma situ, invasive ductal carcinoma, or invasive lobular carcinoma were obtained.

Participants

Patients who were AJCC stage 0 to 3 were included. The patients received adjuvant RT treatment in the Alamal National Hospital, Baghdad Medical City after breast surgery.

Procedure

The patients were either treated in the supine position with 3D-CRT administered daily, Sunday through Thursday, as whole breast photon RT using standard or hypo-fractionation. Patients received RT to the breast or chest wall or breast+LN or chest wall+LN.

Outcome

Acute skin toxicity was measured as erythema or dry desquamations or moist desquamation or pigmentation or pain or itching or bleeding or ulceration.

Statistical Analysis

Descriptive data were summarized using means and standard deviations for continuous data and percentages for categorical data. For both univariate and multivariate analysis of correlates of dermatitis with categorical or continuous correlates. Odds ratios for the relationship between dermatitis and risk factors from the regression model by using SPSS v22. $p < 0.05$ was deemed significant.

RESULTS

Patient, Tumor, Skin toxicities, and Treatment Characteristics

Most of women enrolled in this study belong to the age above 45 years as 68.2%. Housewife represented in 70.1% of women. There were 14% of patients uneducated. 82.8% of women studied were married. Most of patients have 1-5 children as 62.5%. Women smoker were 10.8%. Menopause women were 43.9%, whereas post-menopause were 56.1%. Diabetic women were 16.8%. Hypertension found in 28.9%. Women suffered from CHD were 10.1%. Women taller than 160 cm were 64.7%. Most patients were weigh 50 Kg-100 Kg, were 92.9%. The common BMI recorded was within normal limit as 37.2%, followed by overweight 32.7%, as showed in Table1. The most common grade of breast cancer in this study were grade II 44.6% and grade III 47.4%. Mastectomy plus ALND was the common surgical procedure in 82.8% of patients. Most of the patients received ChX and RT postoperatively. The chest wall plus axillary area was the common site of RT in 63.1%, followed by the breast plus axillary region in 28.7%. The 4050cG/15F was the common RT dose utilized. Regard photon energy, the 6 MeV was applied in 68.2% of patients, while 10 MeV used only in 20.4%. The white skin presented in 27.4% of patients, whereas brown color was prominent in 67.5%, in addition the black colour found in 5.1% of women only. The most duration of the sequel of skin toxicities was at 2 weeks of RT in 43.9%, followed by 3 weeks as 23.6%. The dermatological manifestations recorded in 72.6% of women exposed to RT as showed in Table 2. Erythema of the skin presented in 59.9% of patients. Pigmentation or discoloration of the skin found in 28% of women. Women suffered from itching were 21%. Pain felt by 19.75 patients. Dry desquamation seen in 31.2% patients, whereas moist skin was occurring in 5.7% of women. We noticed skin ulcer in 2.5% of population (Table 3). Nearly, all skin manifestations of toxicities mostly seen in old women; who have work outside home; of low education level; married; those have more one child; smoking; diabetic; hypertensive; those with CHD history; those taller than 160 cm; obese; those with abnormal BMI; high grade diseases; those underwent MRM+ALND; those received ChX; those who received RT on the chest wall+axillary; those received dose of 40G/15F; utilized of photon energy 6 MeV; those have brown skin, showed in Table 4.

Univariate analysis of risk factors

Univariate analysis was performed to determine if age, employments, education, marital status, parity, menopause status, weight, height, BMI, grade of breast cancer, types of surgery, RT sites, How much of photon energy, skin color types, RT dose fractionation, onset of toxicities, chemotherapy use, smoking status, history of diabetes mellitus, history of hypertension, and coronary HD were risk factors, showed in Table 5. Weight was related to skin manifestation, with Odds ratios being the fold-increase in Odds for every 10 Kg increase in weight (OR 0.676, 95% CI 0.02-16.89, p=0.008). In addition, for a 1-unit increase in BMI, skin toxicities was more likely (OR 0.609, 95% CI 0.31-1.12, p=0.0015). For those underwent MRM were more suffering from skin toxicities compared to those underwent BCS (OR 4.488, 95% CI 1.28-15.74, p=0.019). Regarding sites of RT, chest wall when exposed to RT was more liable to develop dermatitis than breast alone (OR 0.322, 95% CI 0.14-0.76, p=0.01). When women received hypo-fractionated RT, they were less likely to have skin dermatitis (OR 0.211, 95% CI 0.06-0.74, p=0.0015). All the rest factors did not affect risk for development of skin toxicities sequel.

Multivariate analysis of risk factors

Multivariate analysis assessed variables significant in the univariate analysis including BMI, fractionation schedule, surgery types, sites of RT, and weight. The variables selected did not pass the p-value test for multivariate analysis, which included weight, types of surgery, and sites of RT. The higher risk of toxicities (OR 1.09, 95% CI 1.01-1.11, p<0.000) persisted with increasing BMI. The standard breast dose still increased the risk of dermatitis (OR 0.05, 95% CI 0.04-0.51, p<0.000), in comparison to the hypo-fractionated RT (Table 6).

Tab. 1. Demographic features of women of the study

Characteristics		N (%)	Mean±SD
Age (years)	<45	50 (31.8)	48.77 ± 10.35 (49)*
	>45	107 (68.2)	
Employments	Yes	47 (29.9)	
	No	110 (70.1)	
	Not	22 (14)	
Education level	Primary	50 (31.8)	
	Secondary	41 (26.1)	
	High	44 (28)	
Marital status	Married	130 (82.8)	
	Single	10 (6.4)	
	Divorced	3 (1.9)	
	Widow	14 (8.9)	
Parity (No. of children)	0	25 (15.9)	
	1-5	98 (62.5)	
	6-10	32 (20.3)	
	>10	2 (1.3)	
Smoking	Yes	17 (10.8)	
	No	140 (89.2)	
Menopause status	Menopause	69 (43.9)	
	Post menopause	88 (56.1)	
DM	Yes	25 (16.8)	
	No	124 (83.2)	
HTN	Yes	43 (28.9)	
	No	106 (71.7)	
Coronary HD	Yes	15 (10.1)	
	No	134 (89.9)	
Height (cm)	<160 cm	55 (31.8)	160.35 ± 7.12
	>160 cm	101 (64.7)	
Weight (Kg)	<50	1 (0.6)	71.97 ± 15.86
	50-100	145 (92.9)	
	>100	10 (6.4)	
BMI (m^2/Kg)	Underweight (<18.5)	2 (1.3)	27.98 ± 6.26 (26.5)*
	Normal (18.6-24.9)	58 (37.2)	
	Overweight (25-29.9)	51 (32.7)	
	Moderate obesity (30-34.9)	24 (15.4)	
	Sever obesity (35-39.9)	11 (7.1)	
	Morbid obesity (>40)	10 (6.4)	
Total		157	
*median			

Tab. 2. Breast cancer features of the study

Characteristics		N (%)
Grade	I	8 (5.1)
	II	70 (44.6)
	III	76 (47.4)
Surgery types	Mastectomy+ALND	130 (82.8)
	Mastectomy	1 (0.6)
	BCS+ALND	26 (16.6)
Chemotherapy	Yes	153 (97.5)
	No	4 (2.5)
RT	Yes	154 (98.1)
	No	3 (1.9)
Sit of RT	Breast	2 (1.3)
	Breast+Axillary	45 (28.7)
	Chest wall	8 (5.1)
	Chest wall+ Axillary	99 (63.1)

RT doses	5000cG/25F	27 (17.2)
	4050cG/15F	127 (80.9)
Photon energy (MeV)*	6	107 (68.2)
	10	32 (20.4)
Skin color type	White	43 (27.4)
	Black	8 (5.1)
	Brown	106 (67.5)
	Not	43 (27.4)
Duration onset of skin toxicities	1	3 (1.9)
	2	69 (43.90
	3	37 (23.6)
	4	4 (2.5)
	5	1 (0.6)
Side effect	Yes	114 (72.6)
	No	43 (27.4)
Total		157
*missing records		

Tab. 3. Skin toxicities features of the study

Characteristics		N (%)
Erythema	Yes	94 (59.9)
	No	63 (40.1)
Pigmentation	Yes	44 (28)
	No	113 (72)
Itching	Yes	33 (21)
	No	124 (79)
Pain	Yes	31 (19.7)
	No	126 (80.3)
Dry desquamation	Yes	49 (31.2)
	No	108 (68.8)
Moist desquamation	Yes	9 (5.7)
	No	148 (94.3)
Ulceration or bleeding	Yes	4 (2.5)
	No	153 (97.5)
Total		157

Tab. 4. Skin toxicities manifestations after postoperative RT in women with breast cancer

		Erythema	Pigmentation	Itching	Pain	Dry desquamation	Moist desquamation	Ulceration or bleeding	p-value
		%							
Age	<45 year	19.7	8.9	8.3	7.6	8.3	1.9	1.9	0.053
	>45 year	40.1	19.1	12.7	12.1	22.9	3.8	0.6	
Employments	Yes	41.4	19.1	15.9	12.7	23.6	2.5	1.9	0.06
	No	18.5	8.9	5.1	7	7.6	3.2	0.6	
Education level	Yes	6.4	1.9	2.5	2.5	4.5	0.6	0	0.055
	No	53.5	26.1	18.5	17.2	26.7	5.1	2.6	
Marital status	Yes	47.2	21	17.8	17.2	25.5	5.1	1.9	0.071
	No	12.7	7	3.2	2.5	5.7	0.6	0.6	
Parity	Yes	44.1	25.6	21	19.7	31.2	5.7	2.5	0.089
	No	15.8	2.4	0	0	0	0	0	
Smoking	Yes	50.3	21	14.6	14	24.8	5.1	1.9	0.05
	No	9.6	7	6.4	5.7	6.4	0.6	0.6	
Menopause	Menopause	26.8	13.4	10.2	9.6	10.2	2.5	1.9	0.19
	Post-menopause	33.1	14.6	10.8	10.2	21	3.4	0.6	
DM	Yes	49	22.1	16.1	14.8	20.8	3.4	2	0.05
	No	10.1	5.4	4.7	4.7	8.1	2	0	
HTN	Yes	42.3	18.1	14.1	12.8	16.8	4.7	2	0.045
	No	16.8	9.4	6.7	6.7	12.1	0.7	0	

Coronary HD	Yes	53	22.1	17.4	18.1	24.2	5.4	2	0.066
	No	6	5.4	3.4	1.3	4.7	0	0	
Height	<160 cm	19.9	7.7	9	7.1	13.5	3.2	1.3	0.059
	>160 cm	39.7	19.9	11.5	12.8	17.9	2.6	1.3	
Weight	50-100 Kg	55.8	26.3	18.6	17.9	29.5	5.1	2.6	0.01
	>100 Kg	3.2	1.3	1.9	1.9	1.9	0.6	0	
BMI	Normal	19.9	10.9	9	7.7	8.3	0.6	0.6	0.001
	Abnormal	39.7	16.7	11.5	12.2	23.1	5.2	2	
Grade	II	24.8	13.1	10.5	9.2	11.8	0.7	1.3	0.05
	III	30.1	13.1	9.2	10.5	17	3.9	0.7	
Surgery types	MRM + ALND	45.2	19.1	16.6	15.3	24.2	2.5	1.3	0.000
	BCS + ALND	14	8.3	3.8	3.8	6.4	3.4	1.3	
ChX	Yes	58.6	26.8	21	19.1	30.6	5.7	2.5	0.047
	No	1.3	1.3	0	0.6	0.6	0	0	
RT sites	Breast+ Axillary	21	8.9	4.5	5.7	9.6	3.2	0.6	0.001
	Chest wall + Axillary	32.5	17.8	13.4	12.1	17.2	2.5	1.9	
RT doses	50G/25F	15.3	9.6	5.7	5.7	6.4	2.5	0.6	0.000
	40G/15F	44.6	18.5	15.3	14	24.8	3.2	1.9	
Photon energy	6 MeV	46.8	21.3	18.4	15.6	24.8	3.5	1.4	0.001
	10 MeV	11.3	7.8	4.3	5.7	6.4	1.4	0.7	
Skin color type	White	18.5	12.7	8.3	8.9	10.2	0.6	0.6	0.05
	Black	3.8	2.5	1.9	1.9	1.3	0	0	
	Brown	37.6	12.7	10.8	8.9	19.7	5.1	1.9	

Tab. 5. Univariate analysis of risk of skin toxicities factors after postoperative RT in women with breast cancer

	Definition	OR	95%CI	p-value
Age	Odds ratio of skin toxicities after RT for a 5 year increase in age?	0.968	0.47-1.99	0.929
Employments	Odds ratio of skin toxicities after RT was high for women who have work **vs** unemployed women?	1.038	0.5-2.16	0.92
Education level	Odds ratio of skin toxicities after RT was high for uneducated women **vs** well educated women?	2.375	0.95-5.92	0.063
Marital status	Odds ratio of skin toxicities after RT was high for married women?	0.415	0.14-1.17	0.096
Parity	Odds ratio of skin toxicities after RT was high for women have more one child?	1.306	0.59-2.87	0.505
Smoking	Odds ratio of skin toxicities after RT was high for smoking women **vs** non-smoker women?	4.038	0.88-18.37	0.071
Menopause	Odds ratio of skin toxicities after RT was not changed for menopause women **vs** post-menopause women?	1.05	0.53-2.06	0.887
DM	Odds ratio of skin toxicities after RT was high for DM **vs** no DM?	1.414	0.55-3.65	0.473
HTN	Odds ratio of skin toxicities after RT was high for HTN **vs** no HTN?	0.96	0.46-2.02	0.915
Coronary HD	Odds ratio of skin toxicities after RT was high for CHD **vs** no CHD?	1.045	0.34-3.24	0.939
Height	Odds ratio of skin toxicities after RT for a 10 cm increase?	1.002	0.49-2.02	0.995
Weight	Odds ratio of skin toxicities after RT for a 10 Kg increase?	0.676	0.02-16.89	0.008
BMI	Odds ratio of skin toxicities after RT for a 1 unite increase?	0.609	0.31-1.21	0.0015
Grades	Odds ratio of skin toxicities after RT was high for high grade diseases?	1.325	0.66-2.67	0.429
Surgery types	Odds ratio of skin toxicities after RT was high for MRM **vs** BCS?	4.488	1.28-15.74	0.019
ChX	Odds ratio of skin toxicities after RT was high for ChX **vs** no ChX?	0.687	0.07-6.78	0.75
RT sites	Odds ratio of skin toxicities after RT was high for chest wall **vs** breast?	0.322	0.14-0.76	0.01
RT doses	Odds ratio of skin toxicities after RT was high for standard dose **vs** hypofractionation dose?	0.211	0.06-0.74	0.0015
Photon energy	Odds ratio of skin toxicities after RT was high for 6 MeV **vs** 10 MeV?	1.603	0.71-3.63	0.257
Skin color type	Odds ratio of skin toxicities after RT was high for brown **vs** white **vs** black skin?	0.529	0.23-1.13	0.099
Onset of side effect	Odds ratio of skin toxicities after RT was increase in 2 week duration?	2.75	0.62-12.13	0.182

Tab. 6. Multivariate analysis of risk of skin toxicities factors after postoperative RT in women with breast cancer

	Definition	OR	95%CI	*p*-value
Weight	Odds ratio for a 10 Kg increase?	0.889	0.77-1.43	0.092
BMI	Odds ratio for a 1 unite increase?	1.09	1.01-1.11	0.000
Surgery types	Odds ratio was high for MRM vs BCS?	2.321	0.88-11.52	0.066
RT sites	Odds ratio was high for chest wall vs breast?	0.505	0.33-0.89	0.054
RT doses	Odds ratio was high for standard dose vs hypo-fractionation dose?	0.05	0.04-0.51	0.000

DISCUSSION

Regarding all demographic characters of patients, breast cancer features, and treatments modalities were seem to be as same as for all studies conducted in Iraq [1-5]. Over the years, there was a significant progress had made for reducing potential toxicities of EBRT after breast surgery to decreased skin toxicities as a one of major unwanted side effect. There are now improved radiation techniques as 3D-CRT and IMRT, which allow for better dose homogeneity [10,11]. Hypo-fractionated schedule of RT to the breast have been found to have better long-term cosmetic outcomes in most randomized control trials [12]. Despite these, patients continue to frequently have acute skin reactions when undergoing breast RT. Many researchers studied radiation fractionation schedule, patient position, 3D-CRT, IMRT, concomitant hormone treatment, and patient-related factors including high BMI, large breast volumes, smoking, and single nucleotide polymorphisms in genes involved in DNA repair pathways. They found that standard fractionation schedules, 3D-CRT technique compared to IMRT, largest breast size, high BMI, and smoking, were increased risk of acute dermatitis [10,13-15]. Acute radiation dermatitis is a common side effect of RT in many forms of cancer including breast cancer. The severity of the reaction may depend on the RT fraction schedules, the total dose, the treated skin area, and also individual variations [16]. The short of blood supply, postoperative breast cancer chest wall skin is not well tolerated, and easy to injury in the radiation field of skin, as manifested by erythema, edema, erosion, ulcer, or even serious [16].

In our study, BMI, and radiation fractionation schedule appeared to be the most significant factors for development of post radiation dermatitis. In addition, a hypo-fractionated course of RT seem to be of benefits for decreasing skin toxicities risk and would support using this regimen over a standard fractionated course of RT. Though other factors were not analyzed on multivariate analysis due to smaller sample size of patients, it may be a significant risk factor for the development of post radiation dermatitis if a large enough sample size of patients can be obtained. The pathophysiology behind that severity of this symptom may be related to the prescription dose and fractionation delivered to the skin and to patient-related factors such as obesity, smoking, and use of radio-sensitizing chemotherapy [17]. The mechanisms may be associated with an inflammatory cascade mediated by cytokines [18], or there were morphologic alterations to the normal histologic characteristics, including a marked decrease in basal cell proliferation, endothelial cell damage, and resultant vasodilation with altered membrane permeability, and inflammatory cytokine release by irradiation [19].

Understanding these statements help radiation oncologist to advice the patients who are more likely to develop these toxicities. Finally, the skin toxicities in adjuvant RT breast cancer patients is generally common. The patients need to be well informed and made aware that any skin reactions will acceptable post RT.

CONCLUSION

RT is an important part in the management of postoperative breast cancer patients. The incidence of postoperative RT-induced skin toxicities is common, and might affect radiation process, and lead to interrupted of patients' schedule. Lower BMI, lower weight, surgery types, RT sites and hypo-fractionated courses were beneficial to decrease skin toxicities risk. The other factors were not significant within our women population

CONFLICT OF INTEREST DISCLOSURES

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