ACUTE RADIOTHERAPY-INDUCED SKIN REACTIONS: THREE MONTHS CLINICAL OBSERVATION AT A SINGLE INSTITUTE IN KURDISTAN-IRAQ

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ABSTRACT

Background

Radiotherapy Induced Skin Reactions (RISR) are common side effects of external-beam radiotherapy (EBRT). They can be acute or chronic and may require special attention by the care givers. It is not yet studied in our region.

Objectives

To observe the clinical manifestations of randomly collected patients, whom will take RT in a single radiation oncology center, over a period of three months post the first RT fraction.

Methods

Fifty patients with different types of cancers participated, whom have been treated with EBRT for different intentions. Ten sessions of clinical observation applied, started before the 1st EBRT dose and extended to 12th week, using Skin Toxicity Assessment Tool (STAT).

Results

It involved 35 females and 15 males. Full assessment was amenable for 49 patients. Breast cancer patients were half of the cohort. Seventy percent of participants received a total dose of 4001-6000 centyGray (cGy). Ninety four percent got at least one of RISRs ranging from faint erythema 94%, itching 82%, hyperpigmentation 78%, dry desquamation 74%, burning 66%, bright erythema 62%, wet desquamation 58%, tenderness 30%, and ulceration 6%.

Conclusion

Acute RISR is a very common side effect of EBRT in our population. Erythema was the most frequent, while ulceration was the lowest. Total dose was directly proportional to the severity of damage.

Keywords: *Cancer, Radiotherapy Induced Skin Reactions, Kurdistan, Iraq.*

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INTRODUCTION

The radiotherapy (RT) term was introduced by Emil Grubbe, a medical student used X-rays to treat a female patient with recurrent breast carcinoma in 1903, after Rontgen's discovery of X-ray in 1895 [1-3]. RT can be used as external beam radiotherapy (EBRT), the most common modality of RT that is delivered with a source-skin distance of 80-100 cm. Although, treating malignancies is a function of teamwork, in the modern oncology field, RT is crucial, since half of all cancer cases require it [4-8]. It is given for cure, prophylaxis, immune-modulation and palliation [4, 9] . About 57% of the total cancer cases occur in low- and middle-income countries [10-11]. RT is highly effective to permanently inactivate cancer stem cells (CSC), through which permanent local control could be achieved [5-12].

The cells and tissues in the body have different radiosensitivity properties [13]. The skin is a highly radiosensitive organ [14, 15]. The other radiosensitive sites include mucosal surfaces, bone marrow, muscle, brain tissue, reproductive and gastrointestinal tract [15, 16]. Radiation causes stem cells death, and significant alterations at molecular, gross, and functional levels [3, 5,17]. Now, RISR is quite common after RT, it affects 95 % of the patients [6, 18]. Those having breast, anal, vulval, head and neck cancers are more prone to get RISRs [19, 20]. After applying RT free radical forms and double-stranded breaks in nuclear and mitochondrial DNA occur irreversibly, with subsequent inflammation of the skin cellular elements and vasculature [13, 14, 21, 22].

Radiotherapy-induced skin reaction is also called radiation dermatitis or radiodermatitis, it can be acute or chronic [1, 14]. The acute one occurs within hours up to 3 months post treatment, whereas the chronic one manifests months to years after RT [1, 3, 13, 14, 19]. Clinical manifestation of RISR varies; it includes redness, dry desquamation, moist desquamation, and ulceration [1, 6, 18, 23]. Symptoms are feeling of tightness feeling, pain, and itching [6]. The other acute skin changes include swelling, hyperpigmentation and loss of hair [14] .

Both the patient and treatment characteristics affect the extent of RISRs [3, 14, 18, 19, 24] . Treatment-related factors include fraction size, energy type, total dose, anatomical location, field size, concurrent chemotherapy, and the use of bolus; a material used to provide build-up of dose to the skin surface [24-28]. Patient factors are age, race, ethnicity, genetics, skin status, medical diseases, weight, sun exposure, drugs, and smoking [24, 28, 29].

Despite of availability of several systems, till now no single one has been accepted worldwide to measure the RISRs [14, 30] . However, Berthelet et al (2004) validated STAT scale for clinical and research purposes [31].

To the best of our knowledge, in our locality till now, acute RISRs had not been studied. It is reported by Ryan et al. (2007) that beside comorbid medical diseases, race and ethnic background affect the severity of RISRs [32]. Thus observing these reactions in a known community that reflects specific race and ethnicity may worth a trial of study. This study aims at observing the clinical manifestations of randomly collected patients, whom will take RT in a single radiation oncology center, over a period of three months after the first RT fraction.

METHODS

An observational cross-sectional study has been approved by (Kurdistan Board for Medical Specialties); it matches all the regulations by (Directorate of Training Affairs-Scientific Research Units) per its research protocol. The study has been executed at a single radiation oncology unit; Zhianawa Cancer Center-Sulaimani – Iraq.

We excluded age < 16 years old, previous RT, brachytherapy, patients who were unconscious, mentally retarded, in an emergency medical setting, pregnant and lactating.

Informed consent was provided. The duration of the study per each single participant's follow up was 3 months from the first fraction. It started from May 31, 2017, and the data collection closed on January 10, 2018.

We used STAT scale to measure the RISRs, as shown in (Appendix 1). On the first day of the treatment, before taking the first fractionated dose, we examined the participants, looking for any sign of skin change in color, integrity, and appearance. After the 1st fraction, immediately the site was rechecked to see any noticeable change. The total dose of the course was fractionated. The patients had been taking each fraction on a daily base, no more than 5 days a week. Each single patient was followed for signs and symptoms of RISRs and were documented.

After initiation of the radiation therapy, we started checking the participants according to the STAT scale, on a weekly bases. The follow up process included ten visits. The first checkup is the pre-treatment assessment, and then sequentially the checkup performed on 1st,

2nd, 3rd, 4th, 5th, 6th, 7th, 8th and 12th week post radiation initiation (i.e., 1st RT fraction). Each patient got his/her own profile and updated on each visit.

The statistical analysis was performed by SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences). The data presented in tabular forms showing the frequency and relative frequency distribution of different variables. Chi-square tests were used to compare the categorical data (i.e. between certain variables as skin type or treatment site and different effects as itching, erythema, etc.). For comparing the quantitative variables as the doses of RT and their effects, T test and ANOVA were used by comparing their arithmetic means. P values of 0.05 were used as a cut off point for significance of statistical tests.

RESULTS

The study population includes 50 patients. Thirty percent were males and seventy percent were females. The population characteristics are shown in (Table 1). Apart from a patient who passed away after 2 months of RT initiation due to the original disease, the remaining patients committed to the treatment course and the study follow up. Different clinical cases included in the study due to randomization, the detail of which is shown in (Table 2). The minimum total dose applied was 800 cGy, and the maximum was 6600 cGy. For 70% of the participants the total dose ranged between (4001-6000) cGy, and the dosimetry detail is provided in (Table 3).

Faint erythema was the earliest to appear, affecting 20% of patients, as early as 1st week post radiation initiation, followed by dry desquamation 14%, bright erythema 4%, and hyperpigmentation 2%, but moist desquamation appeared from the 3rd week onwards. In (Table 4) the rate of occurrence of each reaction is shown.

The rate of erythema occurrence increased rapidly on the 2nd week. On the 5th week, majority of the cases were having different degrees of redness. From the 7th week onwards, redness started to disappear, however at the end of the study, 30% still continued to have erythema. During the whole study period, 3 cases did not develop any clinically apparent erythema. The highest rate of occurrence for dry desquamation was during the 3rd week, affecting 40% of patients, while wet desquamation affected majority during the 5th week, affecting 46% of them. The rate of occurrence of other objectively-measured RISRs per each week of follow up is provided in (Table 5).

Burning and itching were reported as early as 1st week at a frequency of 10% and 8% respectively. On the 5th week, itching and burning reached their peak in term of frequency of occurrence (76% and 66%), respectively. At the end of the study 6 (12%) patients left with some degree of burning, and 17 (34%) patients with variable degrees of itching. Tenderness affected 28% of the patients on the 5th week, and 6 of them were still suffering from tenderness on the 12th week. No pulling reported in breast cancer cases.

Table 1. Patient characteristics.

Variable		Frequency	Percentage
Age	16 - 35 Years	8	16%
	36 - 50 Years	20	40%
	51 - 65 Years	10	20%
	66 - 88 Years	12	24%
Gender	Male	15	30%
	Female	35	70%
Fitzpatrick Skin type	Two	7	14%
	Three	16	32%
	Four	27	54%
Ethnicity & Race	Kurds (Caucasian race)	46	92%
	Arabs (Caucasian race)	4	8%
Aim of treatment	Curative	39	78%
	Palliative	11	22%
Boost	Yes	15	30%
	No	35	70%
Bolus	Yes	13	26%
	No	37	74%
Smoking	Yes	11	22%
	No	39	78%
DM	Yes	2	4%
	No	48	96%
Chemotherapy	Yes	28	56%
	No	22	44%
Hormone therapy	Yes	11	22%
	No	39	78%
Treatment site	Breast/Chest wall	29	58%
	Head	4	8%
	Neck	5	10%
	Back	8	16%
	Abdomen and pelvis	4	8%

Table 2. Clinical diagnosis of the participant patients.

Diagnosis	Frequency	%	Diagnosis	Frequency	%
Ca breast	29	58%	**Cavernous hemangioma**	1	2%
Hematological	3	6%	**Glioblastoma**	1	2%
Ca larynx	2	4%	**Pituitary adenoma**	1	2%
Ca prostate	2	4%	**Retroperitoneal sarcoma**	1	2%
Ca esophagus	1	2%	**Bronchogenic carcinoma**	1	2%
Ependymoma	1	2%	**Secondaries to lung**	1	2%
Thymoma	1	2%	**Secondaries to liver**	1	2%
Duodenal carcinoma	1	2%	**Secondaries to vertebrae**	3	6%

Table 3. Treatment characteristics.

Dosimetry characteristics		Frequency	Percentage
Total dose/cGy	800 – 2000	9	18%
	2001 - 4000	4	8%
	4001 - 6000	35	70%
	>6000	2	4%
Number of fractions	1 - 5	9	18%
	12 - 20	33	66%
	21 - 33	8	16%
Dose (cGy) / fraction	180 - 200	10	20%
	225 - 300	17	34%
	330 - 800	23	46%

Table 4. Frequency and percentage of radiation-induced skin reactions.

Skin reactions	Number of patients affected	Percentage
Faint erythema	47	94%
Hyperpigmentation	39	78%
Dry desquamation	37	74%
Bright erythema	31	62%
Wet desquamation	29	58%
Ulceration	3	6%
Itching	41	82%
Burning	33	66%
Tenderness	15	30%

Table 5. Frequency of objectively-measured RISR in a given week.

Objective signs		Basal data	1st wk	2nd wk	3rd wk	4th wk	5th wk	6th wk	7th wk	8th wk	12th wk
Erythema	**No**	50	40	25	14	10	7	7	10	16	34
	Faint	0	10	23	31	22	17	24	30	29	14
	Bright	0	0	2	5	18	26	19	10	4	1
Desquamation	**No**	50	50	43	27	20	16	14	16	21	29
	Dry	0	0	7	20	16	11	17	24	26	19
	Wet	0	0	0	3	14	23	18	10	2	1
Exudates	**Yes**	0	0	0	3	14	22	17	9	2	2
	No	50	50	50	47	36	28	32	40	47	47
Hyperpigmentation	**No**	50	50	49	36	23	17	12	11	11	14
	Yes	0	0	1	14	23	33	38	39	38	35

DISCUSSION

Participants' random selection led to involve different anatomical locations in the study (Table 1). During 90 days of follow up, 94% developed at least one of RISRs, with variable degrees of severity, which matches what has been concluded by each of McQuestion et al (2011), and Ryan JL (2012) [14, 18]. Salvo et al (2010) validates that even with the modern techniques of RT, the RT incidence reaches 85% [19].

Erythema was the 1st to appear, it affected 47 patients (94%), compared to Chan et al (2012), is the same [33]. During the 1st week only 10 patients (20%) were having transient and faint erythema, this supports the conclusion by both Simonen et al (1998) and Schmuth et al (2001) [34, 35]. On the 2nd week, the erythema frequency increased obviously, affecting 25 patients (50%), reaching to 86% during 5th and 6th week, appearance of this 2nd round of redness acknowledged by Kupper et al (1990) [36]. We correlate this escalation in the frequency of erythema reaction to the increased dose of the radiation energy perceived by the treated area.

On the 1st week, erythema appeared at a mean total dose of (1409 ± 390; n= 10, p= 0.76), then on the 2nd week at a mean total given dose of (2705 ± 528; n= 23, p= 0.22). By coming to the 5th week when highest number of patients presented with erythema, the mean of total given dose reached (3861 ± 1273; n= 17, and (4474 ± 727, n= 26) for both faint and bright erythema respectively. Both Feight et al (2011), and Glover and Harmer (2014) state that at a mean dose of 2000-4000 cGy erythema reaction appears, thus our results supports their findings [24, 37].

On the 2nd week when the total given dose reached (2304 ± 491; n= 7), dry desquamation started to appear, and the frequency increased significantly on the 3rd week (4182 ± 893; n= 20). In a review Ryan JL (2012) states that dry desquamation starts to appear 3-4 weeks post radiation, and when the total given dose reaches 2000-2500 cGy, while each of Feight et al (2011), and Glover and Harmer (2014) concludes dry desquamation to appear at a dose > 3000 cGy. We observed the higher the dose we applied, the clinical presentation of the underlying skin damage was more severe, going beyond the redness of the skin to desquamative changes.

Hyperpigmentation affected only 1 patient on the 2nd week, increased to affect 14 patients (28%) on the 3rd week at a mean dose of (4576 ± 939; p< 0.001), this result didn't match with a review by Ryan JL (2012), who acknowledges that hyperpigmentation starts to appear at a mean total dose of 1200-2000 cGy within 2-3 weeks of radiation therapy, however the estimated time of occurrence was the same. Totally (78%) of the study population afflicted by hyperpigmentation, which was the highest incidence of RISRs after erythema reactions. The vast majority of our population was of Fitzpatrick skin type 3 and 4, and this best explains why hyperpigmentation rate was obviously high.

All of our breast cancer patients (n=29) developed faint erythema, dry desquamation and hyperpigmentation of variable degrees, and moist desquamation affected 26 (89.6%) patients, supporting Twardella et al (2003) and Vuong et al (2004), who state that breast and skin folds represent one of the most vulnerable sites [29, 38]. However, Fisher et al (2000) states that breast has a high incidence of (30–35%), which is much lower compared to our case [39] . Breast tissue and the skin folds of the intertriginous areas like axilla are among the tissues that are more radiosensitive, in addition these areas are more vulnerable to frictional forces, being moist, and more occluded, all these factors can contribute to the higher frequency and more severity of the radiation reactions.

In a study Mendelsohn et al (2002) estimates the time of occurrence for moist desquamation to be after 4-5 weeks at a total dose of 4000 cGy or more [13]. While according to Ryan JL (2012) will be after 4 weeks or beyond, at a dose of 3000-4000 cGy, but each of Feight et al (2011), and Glover and Harmer (2014) states that at a dose of 4000 cGy or more. By comparing all to ours, in the 3rd week, only 3 patients had wet desquamation, on the 4th week increased to 14 cases at a mean dose of (4267 ± 766 ; p= 0.001), and rate of occurrence peaked during the 5th week at a mean total dose of (4430 ± 732; p< 0.001).

It is stated by Hymes et al (2006) that epidermal layer cell repopulation occurs about the (3rd -5th) week post RT, while complete healing takes place within 4 to 12 months [3]. Compared to our study, the highest rate for healing process start was frankly observed from the 6th week onwards.

In conclusion, we have found that acute RISRs are very common side effects of EBRT using LINAC in patients with Fitzpatrick skin color type 3 and 4, affecting 94% of exposed patients in our locality. Erythema was the most frequent, followed by hyperpigmentation,

desquamative changes and ulceration in decreasing frequency. The higher the total dose, the more severe the skin damage occurred, despite of fractionation. With patient's instruction about the wound care, even without a definite medical prophylaxis, the skin will regain its integrity in the majority of the cases after 3 months. However, hyperpigmentation still persists in many after this period. The radiation reactions are predictable to great extent, regardless of the fractionation, thus having a well-studied modality of probable preventive measures in parallel with skin care practice during and post radiation application might lessen the severity of the RISRs and eventuates in a better compliance to the therapy protocol by the patients.

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Appendix 1. The STAT scale.

Name:	Age:	Sex:	Clinical diagnosis:	
Treatment site:	Filed size:	Energy:	Fitzpatrick skin type*:	
Total dose:	Dose/Fraction:	Fraction No:	Boost:	
Curative:	Palliative:	Routine:	Emergency	Urgent:
Bolus:	Chemotherapy:	Hormone Rx:	DM**:	Smoking:

Weeks		0	1	2	3	4	5	6	7	8	12
Treatment day											
Intact skin (Y/N)											
Erythema	Nil (0) Faint (1) Bright (2)										
Dry desquamation (Y/N)											
Wet desquamation (Y/N)											
Exudate (E) / Others (O)											
Discomforts***	Itching										
	Burning										
	Tenderness										
	Pulling										
	Others										

*Fitzpatrick's skin color type, a numerical classification from 1 through 6, the higher the number, the darker the skin will be.

** Diabetes mellitus

*** Measured using visual analogue scale, higher number means more intense