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Original Article

Acute cutaneous side effects of radiotherapy in patients with pelvic cancer: Frequency, severity and risk factors estimation

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Abstract

Background Radiotherapy is one of the main modalities in the management of cancer along with chemotherapy and surgery. Despite its great benefit it has many side effects on many systems and organs including the skin.

Objective To record the frequency, grades and types of acute cutaneous side effect in patients with pelvic tumors treated with radiotherapy, in order to report the risk factors and to find appropriate strategies for prevention and management.
Patient and methods.

Methods A prospective observational study was carried out in Baghdad Radiation and Nuclear Medicine Centre between August 2020 and August 2021.A total 70 patients were enrolled in this study. All patients had full history and full baseline skin exam and were assessed weekly to record the frequency, types and grades of acute cutaneous side effects till the end of radiotherapy sessions.

Results Seventy patients were enrolled in this study, 42 (60%) females and 28(40%) males with female to male ratio (3:2).there was a statistical significant association between acute cutaneous side effects and overweight ,fair skin type , old age >55 ,combined chemoradiotherapy, high radiotherapy dose and use of bolus, while gender, smoking, surgery, hypertension and diabetes showed no significant association. Four grades of radiodermatitis were observed, grade I (61.43%) , grade II (24.29%) , grade III (8.57%) and grade IV (1.43%) patient.

Conclusion The most common observed side effect was grade I radiodermatitis, factors that might increase risk of cutaneous side effects were overweight, fair skin, older age patients, combined chemoradiotherapy, high radiation dose and use of bolus.

Key words
Side effects; Radiotherapy; Pelvic cancer.

Introduction

Pelvic cancer refers to a variety of malignancies involving the organs and structures in the pelvis.[1] Radiotherapy (RT), is a treatment modality that employs high energy rays or radioactive substances, in order to damage cells of tumor and halt their growth and division.[2]

The international data indicates that fifty percent of cancer patients will receive RT during their illness.[3]

Acute Radiodermatitis, refers to the cutaneous side effects that occurs within the first ninety

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days of radiation therapy, the most frequent consequences include: erythema, desquamation (dry and moist), ulceration and necrosis with the consequent re-epithelialization, post inflammatory hyperpigmentation, reduction, epilation and suppression of sweat and sebaceous glands.[5]

The extent of skin damage depends mainly on two factors: physical properties of the applied radiation on one side and the characteristics of the patient who receives radiotherapy on the other.[5]

- Radiotherapy dose and type
- Radiation field size and site
- Fractionation regimen
- Skin integrity before starting radiation therapy
- Smoking
- Nutritional status
- Age
- Comorbidities[5-7]

Severity grading of radiation dermatitis Multiple grading scales have been used to describe the radiation dermatitis spectrum; however, a gold standard is yet to be established. The most frequently used scales are:

a. the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for acute radiation dermatitis classification and
b. The Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) scale.[8]

Methods

Study design A prospective descriptive study was done at Baghdad Radiation and Nuclear Medicine Center in Medical City complex between August 2020 to August 2021. A total number of 70 patients were enrolled in this study.

Inclusion criteria All patients with histologically confirmed uterine, cervical, vulvar, rectal, urinary bladder or prostatic cancer, that are arranged for radiation therapy.

Exclusion criteria a) History of previous pelvic radiation therapy. b) Dermatological skin disease in pelvic region.

All patient were treated by 3D conformal radiotherapy technique (3DCRT) according to stage of their disease, the number of sessions ranged from 5 to 35 sessions and the patients received 5 sessions weekly from Sunday to Thursday with 2 days off and the dose of radiation ranged from 2000 to 6000 cGy.

The radiotherapy device equipment used was Electa linear accelerator which was established and used since 2015.

The linear accelerator uses microwave technology similar to that use in radars for electron acceleration in a part of the accelerator called the "wave guide" then allows these electrons to collide with a heavy metal target to reproduce high energy x ray which are shaped as they exit the machine to conform to the shape of the patient tumor and the customized beam directed to the patient tumor.

Detailed history was obtained from each patient and include: age, sex, marital status, occupation, type of cancer, history of surgery, chemotherapy, comorbidities, smoking, assessment of BMI (body mass index) and Fitzpatrick skin type.

All patients had full baseline pelvic region skin exam in cooperation with an oncologist and were evaluated weekly throughout treatment to

observe frequency, types and grades of acute cutaneous side effects according to grading criteria based on RTOG (Radiation therapy oncology group)/ EORTC (European organization for Research and Treatment) **(Table 1)**.

Full formal consent was obtained from each patient after explanation goal of the study.

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

Statistical analysis Data analysis and graphics was performed using Statistical Package for the Social Sciences (SPSS) software (version 26, IBM, USA) and Microsoft office (version 2016, Microsoft Corporation, USA).

The data were described using mean, standard deviation, frequency and percentage. Pearson Chi-Square was used to determine the association between the variable factors and dermatitis.

Figure 1 Electa linear accelerator.

Table 1 grading of RD based on RTOG (Radiation therapy oncology group)/ EORTC (European organization for Research and Treatment).[9]

Adverse event	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*	*Grade 5*
Radiation dermatitis	Faint erythema	Moderate-to-brisk erythema	Moist desquamation (other than skin folds and creases)	Skin necrosis	Death
	Dry desquamation	Patchy moist desquamation (mostly confined to sin folds and creases	Bleeding induced by minor trauma or abrasion	Ulceration of full thickness of dermis	
		Moderate edema		Spontaneous bleeding	
Alopecia	Visible on close inspection	Hair loss ≥50% of normal	–	–	–
Atrophy	Associated with telangiectasia or pigmentation changes	Striae or adnexal structure loss	Ulceration	–	–
Induration or fibrosis	Mild, able to pinch skin	Moderate, able to slide skin but unable to pinch	Sever, unable to slide or pinch, limiting self-care	Generalized, impaired breathing or feeding	Death

Table 2 the mean and standard deviation of gender distribution of cases.

	Male		*Female*		*P-value*
Age	Mean 60.29	SD 5.13	Mean 58.29	SD 8.30	0.260

Table 3 Tumor distribution and percentage in this study.

Gender	*Cancer*	*N*	*%*
Female	Uterus	19	45.2
	Cervix	12	28.6
	Vulva	6	14.3
	Rectum	4	9.5
	Bladder	1	2.4
Male	Prostate	11	39.3
	Rectum	9	32.1
	Bladder	8	28.6

Table 4 Patient's demographic characteristics and treatment specifications.

Variable		*Frequency*	*%*
Gender	Male	28	40
	Female	42	60
Smoking	Yes	17	24.3
	No	53	75.7
Hypertension	Yes	15	21.4
	No	55	78.6
Diabetes	Yes	17	24.3
	No	53	75.7
BMI	Overweight or obese	41	58.6
	Normal or low weight	29	41.4
Skin type	II,III	37	52.9
	IV,V,VI	33	47.1
Chemotherapy	Yes	44	62.9
	No	26	37.1
Surgery	Yes	33	47.1
	No	37	52.9

Results

Seventy patients were enrolled in this study, 42 (60%) females and 28 (40%) males with female to male ratio (3:2), mean age for females was 60.29±5.13 and for males was 58.29±8.30 years.

Five different tumor sites were included, the most common observed tumor in females was endometrial Ca (45.2%) followed by cervical (28.6%), vulvar (14.3%), rectal (9.5%) and bladder Ca (2.4%), while in males the most common tumor was prostate Ca (39.3%) followed by rectal (32.1%) and bladder Ca (28.6%).

Table 5 skin reaction grading results.

Dermatitis	Grade			
	I	II	III	IV
Number of patients	43	17	6	1

Regarding patient's demographic characteristics and treatment specifications: Tobacco smoking was observed in 17 (24.3%) patients, hypertension in 15 (21.4%), diabetes in 17 (24.3%), chemotherapy was received in 44 (62.9%), and surgery was done in 33 (47.1%) of patients.

BMI was ≥25 in 41 (58.6%) patients, while in 29 (41.4%) the BMI was < 25.

Regarding Fitzpatrick skin types: 37 (52.9%) were of Fitzpatrick skin type II III and 33 (47.1%) were of type IV V VI.

Four grades of RD were observed 2-4 weeks after starting RT sessions:

Grade I RD presented in 43 (61.43%) of patients **(Figure 2)**.

Grade II RD 17 (24.29%) patients **(Figure 3)**.

Grade III RD 6 (8.57%) patients **(Figure 4)**.

Grade IV RD 1 (1.43%) patient **(Figure 5)**.

Regarding factors that influence the risk of dermatitis:

(1) The following factors showed statistically significant association with the risk of developing dermatitis:

- Body mass index of ≥25 (p-value= 0.00001).

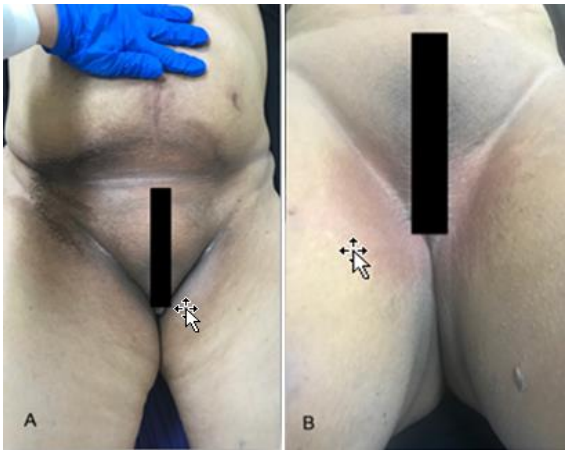

Figure 2 Grade I Radiodermatitis. A Dry desquamation and hyperpigmentation. B Faint erythema.

Figure 3 Grade II Radiodermatitis. A Brisk erythema. B Patchy moist desquamation limited to folds

Figure 4 Grade III Radiodermatitis Confluent moist desqumation outside folds.

Figure 5 Grade IV Radiodermatitis Full thickness ulceration, necrosis and bleeding in the 5th week of treatment sessions.

- Fitzpatrick skin type p II-III (p-value =0.0003).
- Age of patients ≥55 (p-value =0.004).
- Chemotherapy (p-value =0.012).
- High radiotherapy dose ≥50Gy (p-value =0.023).
- Bolus use (p-value =0.042).

(2) While no statistically significant differences between the following factors and risk of having dermatitis:

- Gender (p-value =0.27).
- Hypertension (p-value =0.054).
- Smoking (p-value =0.40).
- Diabetes mellitus (p-value =0.800).
- Surgery (p-value =0.720).

Discussion

Pelvic cancer refers to a variety of malignancies involving the organs and structures in the pelvis.[1] According to Iraqi cancer registry 2020, prostate cancer was the most common pelvic cancer in males, and colorectal cancer was the most common in females.[10]

Table 6 Factors influence the risk of dermatitis.

Variable		*Grade I*	*Grade II*	*Grade III*	*Grade IV*	*P-value*
Gender	Male	21.43	8.57	1.43	1.43	0.27
	Female	40.00	15.71	7.14	0.00	
Age	≥55	51.43	20.00	7.14	0.00	0.004
	<55	10.00	4.29	1.43	1.43	
Smoking	Yes	12.86	4.29	1.43	0.00	0.4
	No	48.57	20.00	7.14	1.43	
Hypertension	Yes	8.57	1.43	1.43	0.00	0.054
	No	52.86	22.86	7.14	1.43	
Diabetes	Yes	14.29	5.71	2.86	0.00	0.80
	No	47.14	18.57	5.71	1.43	
BMI	≥25	48.57	22.86	7.14	1.43	0.00001
	<25	12.86	1.43	1.43	0.00	
Skin type	I,II,III	42.86	18.57	5.71	0.00	0.0003
	IV,V,VI	18.57	5.71	2.86	1.43	
Chemotherapy	Yes	45.71	20.00	8.57	1.43	0.012
	No	15.71	4.29	0.00	0.00	
Surgery	Yes	30.00	12.86	7.14	0.00	0.72
	No	31.43	11.43	1.43	1.43	
Dose	≥50	51.43	22.86	8.57	1.43	0.023
	<50	10.00	1.43	0.00	0.00	
Bolus	Yes	8.57	8.57	7.14	0.00	0.042
	No	52.86	15.71	1.43	1.43	

Surgery, chemotherapy and Radiation therapy are used for treatment of these malignancies, the management is categorized according to the stage at presentation, patient performance status and patient preference, Despite the great benefit of these treatment modalities, they do have disadvantage or side effect.[11]

RD is a cutaneous reaction that occurs as unavoidable side effect of RT during cancer treatment or sometimes after interventional radiology. Radiodermatitis can be classified according to time of occurrence of skin reactions into acute and chronic. The acute reactions develop a few hours to weeks after the first exposure to radiation, whereas the chronic can develop months, years or even decades after radiation. Both acute and chronic RD can have a substantial effects on patients' quality of life and cosmetic outcome.[12]

Regarding the frequency of tumors in pelvic region, in this study the most common tumor in females was endometrial Ca (45.2%), followed by cervical (28.6%), vulvar (14.3%) ,rectal (9.5%) and bladder Ca (2.4%),while in males the most common Ca was prostate (39.3%), followed by rectal (32.1%) and bladder Ca (28.6%), similar results were reported by Al-Rasheed *et al.*[29] (in female endometrial Ca was the most common Ca (50%), followed by cervical Ca (40.6%), while in male the most common Ca was bladder (57.1%), prostate (23.8%)).

The frequency of acute RD of tumors in pelvic region in the current study was 61.43%, parallel studies were done by Bontempo *et al;*[13] the frequency of pelvic tumors acute RD was 48% and in Gonul *et al.* study,[14] the frequency of colon/ prostate Ca RD was 66.7%, While in Al Tai *et al.* study,15 the frequency was 63.8%.

After review of literature and to the best of our knowledge, this is the first study in Iraq, in radiation oncology center and from the dermatological view, and the second study in the world after one Brazilian study, regarding the

types, frequency, and grades of acute RD in pelvic tumors, comparable Iraqi studies were done by Noori *et al;*[16] about RD in head and neck Ca and by Hussein *et al.*[17] about breast Ca.

The severity of skin reactions can be affected by both patient or individual related factors and treatment related factors.

Regarding BMI, in the present study there was a statistical significant association between acute RD and patients with BMI ≥25 (p-value=0.00001). Those results were consistent with Kawamura *et al.*[18] and Bontempo *et al*.[13]

The explanation for this result is that cutaneous folds may be causes of friction, resulting in lesions; this is common in obese people.[61]

For that reason, BMI and body weight can be considered as an evaluative parameter to predict the severity of RD, and the data has shown that obese and overweight patients exhibit higher dermatitis and skin reactions as compared to normal or underweight patients.[19]

In this work, Fitzpatrick skin type I-III showed significant association with RD (p-value=0.0003), which was concordant with Xin *et al.* study.[19]

The mechanism of this side effect because radiation therapy effect on the skin during treatment depends on skin sensitivity to radiation, considering that the principle of the action of rays on the skin is similar to skin reaction caused by solar irradiation.[19]

In this study there was significant association between RD and older age patients ≥55 (p-value=0.004).Similarly, Gonul *et al.*[14] suggest that skin toxicity increased with older age patients >60 years.

The reaction of radiation therapy is depending on the healing ability of skin, which decreases with age, because of low immunity, chronic diseases, alteration in thickness of epidermis, aging of cells, reduction in the capillary network and loss of collagen.

Regarding combination chemotherapy with radiotherapy, the current study showed statistically significant association with risk of RD (p-value=0.012), which was parallel to Bostanoglu study,[29] and gonul *et al.* study.[14]

This is because combining radiation therapy with chemotherapeutic drugs has a strong biologic rationale. Such agents augment radiation effects on skin, reduce the number of cells in tumors undergoing radiation therapy by their independent cytotoxic action and by rendering tumor cells more susceptible to killing by ionizing radiation.[21]

Many agents increase the sensitivity to RT and may enhance cellular damage and reduce tissue repair ability.[22.]

Noori *et al.* reported that a high rate of severe dermatitis observed when RT combined with concurrent chemotherapy.[16.]

The present study showed significant association between high dose ≥50Gy and RD risk (p-value=0.023), and this result was also reported by Gonul *et al*.[14] RD is a dose-dependent toxic effect, and the risk of dermatitis is enhanced by increasing total dose, dose per fraction, and dose volume to surfaces exposed to radiation, because radiation decreases DNA and tissue repair ability.[22]

Regarding bolus effect on skin, this study showed significant association between bolus and RD risk (p-value=0.042), Costa *et al.* reported parallel result about bolus and RD in

breast radiotherapy.[23]

Bolus is a material widely used in practice to alter dosing for targeted radiation therapy, because it has properties equivalent to tissue when irradiated.[24] Bolus condenses energy and increases radiation dose delivered to the epidermis.[25]

Gender, Smoking and comorbidities (hypertension and diabetes mellitus) were not significant with risk of RD (p-value=0.27), (p-value=0.4) (p-value=0.054) (p-value=0.80) respectively. The same conclusion was reported by Gonul *et al*.[14]

Conclusion

1. Radiation dermatitis impacts the quality of life and compromises treatment outcome because of interruption of radiation schedules.

2. Acute cutaneous side effects was observed in more than half of the patients with pelvic tumors receiving radiotherapy, mostly affecting those with high body mass index, Fitzpatrick II _III skin type, older age group more than 55 years, high dose of radiation, bolus use and patients with combined chemotherapy and radiotherapy.

Recommendations

1. More studies with increase in sample size because of technical error during radiotherapy sessions, Covid lockdown, transport difficulties and poor patient's compliance.

2. Increase medical knowledge in patients receiving radiotherapy.

3. Further studies are needed about this disturbing side effect to confirm the results and know more about causes and methods of management.

4. Special attention and frequent examination to patients with high risk factors to radiodermatitis.

5. Adding measures of prevention like topical steroid to see their effect in decreasing the incidence of radiodermatitis.

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