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Study of Patterns of Cutaneous Manifestations in Patients Receiving Radiotherapy: A Cross-Sectional Study

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Abstract

Background and objectives: Radiation therapy is associated with various cutaneous manifestations which may have a severe impact on the quality of life as well as cancer treatment. Hence, it is important to identify the adverse reactions to radiation therapy for assessment and management of the severity of disease. The present study aimed to evaluate the spectrum of cutaneous adversities in patients undergoing radiotherapy.

Materials and Method: This cross-sectional prospective study was conducted on 97 patients with internal malignancies, for approximately 2 years. Clinical history of the patients was collected during the study. The cutaneous features of all the patients were studied clinically and relevant investigations such as potassium hydroxide examination, Tzanck test, Gram's stained smear, hematological and biochemical investigations, skiagrams, venereal disease research laboratory test, and skin biopsy were conducted when required. In addition, radiation dosage, total radiation cycles, duration of treatment, and clinical diagnosis of radiation-induced skin changes were recorded. Chi-Square test was used to check the association between attributes. P value less than or equal to 0.05 was considered statistically significant.

Results: Grade 1 acute radiation dermatitis was found in majority of the subjects. Statistically significant associations between radiotherapy-induced cutaneous adverse effects and gender ($p<0.004$), radiotherapy-induced side effects and involved site of primary underlying malignancy ($p=0.015$), and radiotherapy cycles and cutaneous adverse effects ($p=0.001$) were observed Maximum cases of adverse effects were observed for doses between 3001 cGy and 4000 cGy with a. significant association between the side effects and dosages ($p=0.002$).

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Conclusion: Acute radiation dermatitis was the most common side effect of definitive radiotherapy in this study. Therefore, it necessitates active intervention by a multidisciplinary group to manage both the acute and late effects of radiotherapy on the skin and subcutaneous tissues.

1. Introduction

Radiation therapy or radiotherapy forms an integral component of management in the field of oncology, and approximately three-fourth of the patients diagnosed with cancer receive radiotherapy during their treatment.[1] Cutaneous side effects due to radiotherapy are common and sometimes severe which might lead to a reduction in the treatment duration. Patients with head and neck cancer, breast cancer, sarcoma, and lung cancer are most often affected due to higher radiation doses to the skin.[2-4] Among the cancer patients receiving radiotherapy, 95% will develop some form of radiodermatitis including dry desquamation, erythema, and moist desquamation.[5] Radiotherapy-induced skin toxicities are classified as acute and chronic. Acute radiation dermatitis is one of the most common reactions of radiotherapy and usually occurs within 90 days of exposure, whereas chronic radiation dermatitis develops many years after treatment.[6]

Acute radiation dermatitis manifests as a spectrum of symptoms that range from no cutaneous changes to the severe skin reactions including erythema, burning, pruritus, pigmentation, epilation, hemorrhage, ulceration, and necrosis.[6,7] Acute dermatitis is usually scored by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).[8] The National Cancer Institute has developed 5 criteria for the classification of acute radiation dermatitis: Grade 1 (faint erythema or desquamation); Grade 2 (moderate to brisk erythema or moist desquamation with moderate swelling); Grade 3 (confluent, moist desquamation >1.5 cm in diameter with severe swelling); Grade 4 (skin necrosis or ulceration) and Grade 5 (death).[8] The severity of reaction ranges from mild erythema to moist desquamation and ulceration.[9,10] The reaction usually starts within 1-4 weeks after initiation of radiotherapy and persists during the treatment period.[11] These cutaneous side effects are painful, unpleasant, affect quality of life, and may influence treatment adherence, schedule, and tolerance.[12,13]

Limited clinical studies have been conducted on the cutaneous manifestations of radiotherapy; however, most of the available literature on this subject comprises case reports.[14-17] Hence, an attempt was made to study cutaneous manifestations of internal malignancies in patients who received radiotherapy to fill this lacuna. The present study aimed to evaluate the spectrum of cutaneous adversities in patients undergoing radiotherapy.

2. Materials and Methods

Study design

This cross-sectional prospective study was carried out on patients with internal malignancies at Karad, Maharashtra, India, from May 2014 to May 2016. A total of 97 patients were selected after obtaining a written informed consent. The study was conducted after approval from the institutional ethics committee. Patients were recruited in the study by universal sampling method. Patients who presented with direct or indirect cutaneous manifestations which could lead to diagnosis of underlying malignancy; and those who were willing to undergo relevant investigations like skin biopsy, Tzanck smear, potassium hydroxide (KOH) scrapes, etc., for confirming cutaneous involvement were included. Patients diagnosed with primary cutaneous malignancy; having other systemic diseases which, in view of the investigator, might mimic cutaneous signs produced by malignancy; or not willing to undergo any examination or procedure to confirm the diagnosis were excluded.

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Clinical history of the patients was collected during the study. The cutaneous features of all the patients were studied clinically and relevant investigations such as KOH examination, Tzanck test, Gram's stained smear, hematological and biochemical investigations, skiagrams, venereal disease research laboratory (VDRL) test, and skin biopsies were conducted when required. In addition, radiation dosage, total radiation cycles, duration of treatment, and clinical diagnosis of radiation-induced skin changes were also recorded. The materials required for this study included a digital camera and a dermoscope available in the department.

Statistical analysis

Data was analyzed using R version 4.0.1 statistical software and Excel. Categorical variables were represented by frequency tables. Chi-square test was used to check the association between attributes. *P* value less than or equal to 0.05 was considered statistically significant. The strength of association was measured by Cramer's V/odds ratio.

3. Results

The cutaneous adverse effects of radiotherapy were diagnosed based on the morphology of the lesion. Table 1 presents the distribution of these cutaneous adverse effects. Majority (64.95%) of the cases had Grade 1 acute radiation dermatitis.

Table 1: Cutaneous adverse effects of radiotherapy

Diagnosis	Frequency; n (%)
Faint erythema	19 (19.59)
Grade 1 Acute radiation dermatitis	63 (64.95)
Grade 2 Acute radiation dermatitis	7 (7.22)
Grade 3 Acute radiation dermatitis	2 (2.06)
Grade 4 Acute radiation dermatitis	2 (2.06)
Oral mucositis	4 (4.12)

Age- and gender-based distribution of cutaneous adverse effects of radiotherapy is presented in Table 2. There was no statistically significant association observed between the side effects and age, but the association between side effects and gender was significant ($p<0.004$). The number of adverse effects was more in females (57.7%) as compared to males.

Table 2: Distribution of adverse effects based on age and gender

Variables		Radiotherapy side effects						
Age groups (years)	Count	Faint erythema	Grade 1 ARD	Grade 2 ARD	Grade 3 ARD	Grade 4 ARD	Oral mucositis	Total
<40 y	Count % within age % within RT SE	5 35.7% 26.3%	6 42.9% 9.5%	1 7.1% 14.3%	1 7.1% 50.0%	-	1 7.1% 25.0%	14 100.0% 14.4%
40-49 y	Count	4 18.2%	15 68.2%	2 9.1%	-	1 4.5%	-	22 100.0%

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	% within age % within RT SE	21.1%	23.8%	28.6%		50.0%		22.7%
50-59 y	Count % within age % within RT SE	4 16.0% 21.1%	17 68.0% 27.0%	2 8.0% 28.6%	- 	1 4.0% 50.0%	1 4.0% 25.0%	25 100.0% 25.8%
60-69 y	Count % within age % within RT SE	5 17.9% 26.3%	18 64.3% 28.6%	2 7.1% 28.6%	1 3.6% 50.0%	- 	2 7.1% 50.0%	28 100.0% 28.9%
>70 y	Count % within age % within RT SE	1 12.5% 5.3%	7 87.5% 11.1%	- 	- 	- 	- 	8 100.0% 8.2%
Total	Count % within age % within RT SE	19 19.6% 100.0%	63 64.9% 100.0%	7 7.2% 100.0%	2 2.1% 100.0%	2 2.1% 100.0%	4 4.1% 100.0%	97 100.0% 100.0%
Pearson Chi-square test; p=0.907								
Gender		**Faint erythema**	**Grade 1 ARD**	**Grade 2 ARD**	**Grade 3 ARD**	**Grade 4 ARD**	**Oral mucositis**	**Total**
Male	Count % within age % within RT SE	5 12.2% 26.3%	32 78.0% 50.8%	 	 	 	4 9.8% 100.0%	41 100.0% 42.3%
Female	Count % within age % within RT SE	14 25.0% 73.7%	31 55.4% 49.2%	7 12.5% 100.0%	2 3.6% 100.0%	2 3.6% 100.0%	 	56 100.0% 57.7%
Total	Count % within age % within RT SE	19 19.6% 100.0%	63 64.9% 100.0%	7 7.2% 100.0%	2 2.1% 100.0%	2 2.1% 100.0%	4 4.1% 100.0%	97 100.0% 100.0%
Pearson Chi-square test; p=**0.004**								

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ARD: Acute radiation dermatitis; RT: Reaction time; SE: Standard error

**p≤0.05 considered statistically significant*

Faint erythema was observed in all types of tumors. The different grades of acute radiation dermatitis and the types of tumor/cancer with which they were most commonly associated are as follows: head and neck cancers had Grade 1 dermatitis (57.8%), breast (Grade 2: 85.70%; Grade 3: 50%) and genitourinary tumors (Grade 2: 14.3%; Grade 3: 50%) had both Grade 2 and 3 dermatitis; whereas Grade 4 dermatitis was commonly observed in genitourinary tumors (100%) and oral mucositis in head and neck cancers (100%). The association between radiotherapy adverse effects and the involved site of primary underlying malignancy was statistically significant (p=0.015) (Table 3).

Table 3: Comparison of adverse effects with involved site of primary underlying malignancy

	Type of tumor/cancer	Count	Cutaneous adverse effects						Total
			Faint erythema	Grade 1 ARD	Grade 2 ARD	Grade 3 ARD	Grade 4 ARD	Oral mucositis	
Involved site	Breast tumors	Count	4	19	6	1	0	0	30
		% within involved site	13.3%	63.3%	20.0%	3.3%	0%	.0%	100.0%
		% within diagnosis	22.2%	29.7%	85.7%	50.0%	0%	.0%	30.9%
	Genitourinary tumors	Count	5	3	1	1	1	0	11
		% within involved site	45.5%	27.3%	9.1%	9.1%	9.1%	0%	100.0%
		% within diagnosis	27.8%	4.7%	14.3%	50.0%	100.0%	0%	11.3%
	Head and neck cancer	Count	5	37	0	0	1	4	47
		% within involved site	10.6%	78.7%	0%	0%	2.1%	8.5%	100.0%
		% within diagnosis	27.8%	57.8%	0%	0%	0%	100.0%	48.5%
	Gastrointestinal tumors	Count	2	3	0	0	0	0	5
		% within involved site	40.0%	60.0%	0%	0%	0%	0%	100.0%
		% within diagnosis	11.1%	4.7%	0%	0%	0%	0%	5.2%
	Other	Count	2	2	0	0	0	0	4

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		% within involved site	50.0%	50.0%	0%	0%	0%	0%	100.0%
		% within diagnosis	11.1%	3.1%	0%	0%	0%	0%	4.1%
Total		Count	18	64	7	2	2	4	97
		% within involved site	18.6%	66.0%	7.2%	2.1%	2.1%	4.1%	100.0%
		% within diagnosis	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Pearson Chi-square test; p=**0.015***									

ARD: Acute radiation dermatitis.
**p≤0.05 considered statistically significant.*

Assessment of the cutaneous adverse effects based on histopathology of the primary underlying malignancies showed that Grade 1 acute radiation dermatitis (62.50%) and faint erythema (61.10%) commonly developed in squamous cell carcinomas; Grade 2 (85.7%) and Grade 3 acute radiation dermatitis (50%) in adenocarcinomas; and Grade 4 acute radiation dermatitis and oral mucositis (100%). The association between the side effects and histopathology of the primary underlying malignancy was found to be statistically insignificant.

Comparison of the adverse effects with the dose of radiation received is presented in Table 4. The maximum number (31.6%) of adverse effects was observed for doses in the 3001-4000 cGy range. There was a statistically significant association observed between the side effects and dosages (p=0.002).

Table 4: Comparison of the adverse effects with dose of radiation

Radiation dose (cGy)	**Count**	**Cutaneous adverse effects**						
		Faint erythema	**Grade 1 ARD**	**Grade 2 ARD**	**Grade 3 ARD**	**Grade 4 ARD**	**Oral mucositis**	**Total**
<1000	Count % within dose %within RT SE	4 50.0% 21.1%	3 37.5% 4.8%	1 12.5% 14.3%	-	-	-	8 100.0% 8.2%
1001-2000	Count % within dose %within RT SE	2 18.2% 10.5%	6 54.5% 9.5%	-	-	-	3 27.3% 75.0%	11 100.0% 11.3%

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2001-3000	Count % within dose %within RT SE	5 41.7% 26.3%	7 58.3% 11.1%	-	-	-	-	12 100.0% 12.4%
3001-4000	Count % within dose %within RT SE	6 35.3% 31.6%	11 64.7% 17.5%	-	-	-	-	17 100.0% 17.5%
4001-5000	Count % within dose %within RT SE	-	16 61.5% 25.4%	6 23.1% 85.7%	2 7.7% 100.0%	1 3.8% 50.0%	1 3.8% 25.0%	26 100.0% 26.8%
5001-6000	Count % within dose %within RT SE	2 11.1% 10.5%	15 83.3% 23.8%	-	-	1 5.6% 50.0%	-	18 100.0% 18.6%
>6000	Count % within dose %within RT SE	-	5 100.0% 7.9%	-	-	-	-	5 100.0% 5.2%
Total	Count % within dose %within RT SE	19 19.6% 100.0%	63 64.9% 100.0%	7 7.2% 100.0%	2 2.1% 100.0%	2 2.1% 100.0%	4 4.1% 100.0%	97 100.0% 100.0%
Pearson Chi-square test; p=**0.002***								

ARD: Acute radiation dermatitis; RT: Reaction time; SE: Standard error
**p≤0.05 considered statistically significant*

There was a statistically significant association between the total number of radiotherapy cycles and the cutaneous adverse effects of radiotherapy (p=0.001). Faint erythema was seen at lower fractions and progressed to Grade 1 acute radiation dermatitis as the number of fractions increased (Table 5).

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Table 5: Comparison of adverse effects with total number of fractions received

Radiotherapy cycles	Count	Cutaneous adverse effects					
		Faint erythema	Grade 1 ARD	Grade 2 ARD	Grade 3 ARD	Grade 4 ARD	Oral mucositis
<12	Count % within cycles %within RT SE	9 34.6% 47.4%	13 50.0% 20.6%	-	-	-	-
12-20	Count % within cycles %within RT SE	7 41.2% 36.8%	10 58.8% 15.9%	-	-	-	-
20-24.5	Count % within cycles %within RT SE	2 6.7% 10.5%	20 66.7% 31.7%	-	-	-	-
> 24.5	Count % within cycles %within RT SE	1 4.2% 5.3%	20 83.3% 31.7%	-	-	-	-
Total	Count % within cycles %within RT SE	19 19.6% 100.0%	63 64.9% 100.0%	-	-	-	-
Pearson Chi-square test; p=**0.001***							

ARD: Acute radiation dermatitis; RT: Reaction time; SE: Standard error
**p≤0.05 considered statistically significant*

4. Discussion

Internal malignancies have been on the rise in the recent times with increasing number of malignancies. Many malignancies demonstrate cutaneous involvement which can be detected easily as skin is the most accessible organ, and the change can be diagnosed with minimum investigations. Acute radiation dermatitis is a common side effect of radiotherapy which affects the patients' quality of life and may cause cessation or prolongation of radiotherapy. Cutaneous changes in radiation dermatitis vary with the dose of radiation.

In the present study, the number of radiotherapy adverse effects was high in females as compared to males. Maryum et al's study also reported more number of females with induced skin changes due to radiotherapy.[18] This could be due to the prevalence of breast and cervical cancer in females. With regard to the development of acute radiation dermatitis, males had higher propensity of developing Grade 1 acute radiation dermatitis than females in the current study. Similarly, Saini et al also reported more males with acute radiation dermatitis as compared to females in their study.[19] This difference could be because the malignancy encountered in both sexes is different.

In the present study, Grade 1 acute radiation dermatitis developed most commonly in head and neck cancers whereas Grade 3 was observed most commonly in breast cancers. A study conducted by Bonner et al also reported a similar finding as majority of the patients undergoing radiotherapy for head and neck cancers experienced Grade 1 or 2 radiation dermatitis.[20] Also, a study conducted by Saini et al reported Grade 3 toxicity in breast cancer patients who underwent radiotherapy.[19] Increased involvement of the head and neck area followed by breast in Grade 1 acute radiation dermatitis could be due to increased slope of the skin surface in these areas. The slope of the

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supraclavicular fossa and submental area could create the potential for skin erythema and breakdown most often noted in areas of skin folds.

With regard to the effect of the dose of radiation received, the maximum number of cutaneous reactions including all grades above faint erythema was seen at doses exceeding 4000 cGy. A study conducted by Ding et al on breast cancer patients also reported Grade 2 acute radiation dermatitis at a dosage of >4000 cGy, similar to the current study.[21] Hence, it is proved that extrinsic factors like radiation dose have a high influence on the incidence and severity of radiation-induced dermatitis. Development of oral mucositis in the present study was observed at lower doses between 1001 cGy and 2000 cGy. Various studies have shown that severe oral mucositis occurred in 22-66% of all patients who received radiotherapy for head and neck cancers.[22,23] As observed in our current study, a decline in the number of reactions was observed with reduction in the dosage.

Fractionation allows normal cells time to recover, whereas tumor cells are generally less efficient in repair between fractions. A significant association between the total number of fractions received and cutaneous adverse effects of radiotherapy was observed in the present study. Normally, smaller fraction sizes are associated with reduced incidence and severity of late-onset side effects in normal tissues. The effects of radiation on tissues like nerves, breast, brain, and bones appear late. Consequently, the side effects of radiotherapy are not evident until long after the treatment is over. In our present study, side effects were commonly observed in patients with head and neck cancer and breast cancers. This corresponds with the fact that the total dose received increases with the number of fractions/cycles/visits for cancers like head and neck cancer and breast cancer.

Our study has a few limitations. Firstly, this study had a limited sample size. Secondly, confounding factors like nutritional status, cutaneous markers, infectious diseases, and history of non-specific lesions were not considered in this study. Furthermore, being a cross-sectional study, most of the patients would have been lost to follow-up and hence, the assessment of the outcome of the dermatological changes seen in the affected patients could not be done.

Radiotherapy causes significant acute radiodermatitis and chronic radiodermatitis with associated cutaneous manifestations. This affects patient's quality of life and also hinders treatment schedule. In our present study, acute radiation dermatitis was found to be more common. Patients on radiotherapy require proper monitoring, and careful follow-up is necessary to identify radiation-induced toxicity. Hence, further research on a larger population, with appropriate follow-up and management of these adverse effects to reduce the burden of treatment is warranted.

5. Conclusion

Acute dermatitis due to radiotherapy was the most common side effect observed in almost all patients who underwent radiotherapy, whereas chronic cutaneous reactions were rare. The severity (grade) of radiation dermatitis increased with increasing dose and fractions of radiotherapy as well as areas with folds. Since radiotherapy is an important modality in cancer management, further research on preventive measures is necessary in order to minimize and more effectively manage the cutaneous adverse effects of the therapy.

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