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Various acute cutaneous manifestations in Head and Neck cancer patients treated with radiation therapy

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Abstract
Ionizing radiation (IR) is used to treat a variety of malignant conditions and is used to palliate metastatic disease. However, the development of radiation-induced skin changes is a significant adverse effect of radiation therapy (RT). These complications have a profound effect on patient's quality of life and may also compromise treatment outcomes. There is still paucity of clinical studies on acute manifestations; hence we have considered Head and Neck irradiation for our study group for better understanding of the various cutaneous adverse reactions to radiotherapy. Fifty patients (29 male and 21 female) attending the outpatient clinic in Department of Dermatology, Venereology and Leprosy and Radiotherapy and also inpatients in Radiotherapy wards were enrolled in this study.
Various cutaneous manifestations in head and neck cancer patients following radiotherapy were recorded using the acute RTOG classification in this study. Majority of the patients showed features suggestive of grade 1 acute radiation dermatitis (48%) followed by grade 2 (36%) and grade 3 (16%) whereas none of the patients had grade 4 changes. Among the mucosal manifestations grade 1 was seen in most of the patients (54%). Majority of the patients had no treatment interruption due to radiation toxicity (38%).

Keywords: Radiation dermatitis, radiotherapy, cutaneous reactions, grading, co-morbidities.

Introduction
Radiation therapy is used in a majority of cancer patients at some point during their treatment [1]. Since skin is a continuous organ, radiation at one site can affect skin in other areas.
The severity of the skin reaction ranges from mild erythema and dry desquamation to a more severe moist desquamation and ulceration [2]. High energy radiation is either delivered to the tumor through a machine known as external beam radiotherapy, or by means of a radiation source placed in contact with the tumor, known as brachytherapy [1].
Up to 95% of patients will experience a dose dependent skin reaction at the treated area [3].
Head and neck cancers account for 6% of all cancers worldwide. The distribution of primary tumor sites is: oral cavity (49%), pharynx (23%) and larynx (28%). Patients with recurrent, metastatic disease have a poor prognosis, with a median survival of around 6-7 months. In addition, patients failing first-line therapy have few therapeutic options [4].
Ionizing radiation is an important treatment modality for a variety of malignant conditions. However, development of radiation-induced skin changes is a significant adverse effect of radiation therapy (RT) [5, 6].
Cutaneous repercussions of RT vary considerably in severity, course, and prognosis. Acute changes include erythema and pain and occur within 90 days[7]. Even with modern radiotherapy techniques, approximately 85% of patients will experience a moderate to severe acute skin reaction in exposed areas.
Further studies are needed because these complications have profound effect on patient's quality of life and also may compromise treatment outcomes and due to lack of effective treatment of these adverse effects.

Methodology
Patients receiving radiation therapy for Head and Neck malignancies attending the outpatient clinic in Department of Dermatology, Venereology and Leprosy and Radiotherapy and also inpatients in Radiotherapy wards were included in this study.

Inclusion Criteria

- Patients of both genders of all age groups who are receiving/have received radiotherapy for head and neck cancer sites.
- Patients treated with definitive radiation therapy.
- Patients willing to give informed written consent.

Exclusion Criteria

- Patients having any primary dermatosis.
- Patients with skin manifestations due to other systemic diseases prior to radiotherapy.
- Patients treated with palliative intent.

Method of collection of data

- A total of 50 patients were enrolled in this study.
- Informed written consent of all the patients was taken.
- Predesigned proforma was used to record different findings.
- A detailed history of the disease course, cutaneous manifestations with emphasis on treatment (type of radiation, dosage, and duration) history was taken.
- A complete general physical examination & dermatological examination was done.
- Various cutaneous manifestations were recorded.
- Laboratory investigations based on the cutaneous manifestation were carried out.
- Skin scrapings for fungus
- Swab for culture
- Gram‘s stain
- Tzanck smear
- Complete blood counts
- Renal function tests
- Liver function tests
- Random blood sugar
- Lipid profile
- Skin biopsy

Results

31 patients (62%) of the total 50 underwent adjuvant radiotherapy while the remaining 19 patients (38%) underwent definitive radiotherapy. Most of the patients (86%) were given 3DCRT with 7 patients (14%) receiving IMRT.

The total dose delivered was in the range of 30-70 Gy with a mean of 58.94 Gy and the dose per fraction received by all patients was in the range of 2-3 Gy with 47 patients (94%) receiving 2 Gy, 2 patients (4%) received 3 Gy and 1 patient (2%) received 2.1 Gy. Among the site of treatment 29 patients (58%) received radiation in the head region whereas the remaining 21 patients (42%) received radiation in the neck region.

Use of concurrent chemotherapy was seen in 21 patients (42%) in this study. In this study most of the patients (76%) had no treatment interruption but some of the patients had treatment interruption due grade 3 moist desquamation which was seen in 4 patients (8%) and due to grade 3 mucositis was seen in 8 patients (16%).

The various cutaneous manifestations was recorded using RTOG scoring and accordingly in the skin manifestations, grade 1 was seen most commonly with 24 patients (48%), followed by grade 2 in 18 patients (36%) and grade 3 in 8 patients (16%) while no patients developed grade 4 reactions. Among the mucosal manifestations grade 1 was seen in 27 patients (54%), followed by grade 3 in 6 patients (12%) and grade 2 in 4 patients (8%).

Among the other tissues involved, grade 1 pharynx involvement was seen in 21 patients (42%), followed by grade 2 in only 1 patient (2%) while most of the patients had no involvement of pharynx which was seen in 28 patients (56%). Majority of the patients (70%) did not have any larynx involvement, but some of the patients (28%) showed grade 1 reaction. Salivary gland involvement was seen in 2 patients (4%) with grade 1 reaction. Gram‘s stain was done for 5 patients (10%) who had pustular lesions which showed a few pus cells.

KOH was done for 7 patients (14%) who had scaly lesions, of which 4 patients showed positive for fungal elements.

Table 1: Age Distribution

Age			Skin			
	Grade-1		Grade-2		Grade-3	
	Count	%	Count	%	Count	%
≤ 20	1	4.2%	1	5.6%	0	0.0%
21-30	3	12.5%	2	11.1%	0	0.0%
31-40	3	12.5%	2	11.1%	1	12.5%
41-50	5	20.8%	2	11.1%	4	50.0%
51-60	5	20.8%	8	44.4%	1	12.5%
61-70	5	20.8%	3	16.7%	2	25.0%
71-80	2	8.3%	0	0.0%	0	0.0%
total	24	100.0%	18	100.0%	8	100.0%

Table 2: Gender distribution

Sex			Skin			
	Grade-1		Grade-2		Grade-3	
	Count	%	Count	%	Count	%
Female	14	58.3%	6	33.3%	1	12.5%
Male	10	41.7%	12	66.7%	7	87.5%
Total	24	100.0%	18	100.0%	8	100.0%

Table 3: ECOG

ECOG Performance Status			Skin			
	Grade-1		Grade-2		Grade-3	
	Count	%	Count	%	Count	%
Grade-1	24	100.0%	16	88.9%	7	87.5%
Grade-2	0	0.0%	2	11.1%	1	12.5%
Total	24	100.0%	18	100.0%	8	100.0%

Table 4: Radiation

Radiation			Skin			
	Grade-1		Grade-2		Grade-3	
	Count	%	Count	%	Count	%
Definitive	18	25.0%	9	50.0%	4	50.0%
Adjuvant	6	75.0%	9	50.0%	4	50.0%
Total	24	100.0%	18	100.0%	8	100.0%

Table 5: Treatment Interruption

Treatment Interruption	Skin					
	Grade-1		Grade-2		Grade-3	
	Count	%	Count	%	Count	%
NIL	24	100.0%	14	77.8%	0	0.0%
Yes grade 3 moist Desquamation	0	0.0%	1	5.6%	3	37.5%
Yes grade 3 moist Mucositis	0	0.0%	3	16.7	5	62.5%
Total	24	100.0%	18	100.0%	8	100.0%

Table 6: Skin grading

Skin	Frequency	Percent
Grade-1	24	48.0
Grade-2	18	36.0
Grade-3	8	16.0
Total	50	100.0

Table 7: RTOG grading of Mucosal Involvement

Ucous Membrane	Frequency	Percent
Grade-0	13	26.0
Grade-1	27	54.0
Grade-2	4	8.0
Grade-3	6	12.0
Total	50	100.0

Table 8: Gram's Stain

Gram's Stain	Frequency	Percent
N	45	80.0
P	5	10.0
Total	50	100.0

Table 9: Koh Scrapings

Koh	Frequency	Percent
N	33	86.0
P	7	14.0

Discussion

31 patients (62%) of the total 50 underwent adjuvant radiotherapy while the remaining 19 patients (38%) underwent definitive radiotherapy. Use of concurrent chemotherapy was seen in 21 patients (42%) in this study.

In this study most of the patients (76%) had no treatment interruption but some of the patients had treatment interruption due grade 3 moist desquamation which was seen in 4 patients (8%) and due to grade 3 mucositis was seen in 8 patients (16%) with a significant p value of <0.001. No other study has shown such association with any of the cause for treatment interruption mentioned.

The various cutaneous manifestations was recorded using RTOG scoring and accordingly in the skin manifestations, grade 1 was seen most commonly with 24 patients (48%), followed by grade 2 in 18 patients (36%) and grade 3 in 8 patients (16%) while no patients developed grade 4 reactions.

Among the mucosal manifestations grade 1 was seen in 27 patients (54%), followed by grade 3 in 6 patients (12%) and grade 2 in 4 patients (8%) with significant p value of 0.002. Grade 1 pharynx involvement was seen in 21 patients (42%), followed by grade 2 in only 1 patient (2%) while most of the patients had no involvement of pharynx which was seen in 28 patients (56%) with a significant p value of 0.005. Majority of the patients (70%) did not have any larynx involvement, but some of the patients (28%) showed grade 1 reaction with a significant p value of 0.02.

This finding is similar to as found in study by Krasin *et al.* [7] which showed a significant association between increased grade of skin toxicity and cumulative dose of radiation (p<0.01). However, a study by Kam *et al.* showed that there is no association between dosimetry factors and skin toxicity implying that radiation dermatitis may be dominated by other physical or genetic risk factors that influence individual‘s normal tissue sensitivity [8].

Krasin study also showed the significant positive association of skin toxicity with other factors like total volume of skin treated, use of a bolus dose, Caucasian race and related pain [7].

There are isolated reports of lichen planus confined to radiation therapy site, radiation induced Stevens-Johnson syndrome, erythema multiforme, cutaneous lymphangiectasis, Dariers disease, bullous pemphigoid, vitiligo, discoid lupus erythematosus, localized acneiform eruption, Sweet‘s syndrome, pemphigus, asteotic eczema, non-specific hypersensitivity reaction including urticaria, delayed breast cellulitis. None of the patients in the present study developed these conditions.

In our study four cases of fungal infection limited to the site of radiation was found. Only one similar case has been reported in literature. Five cases of skin pustules and one case of skin fibrosis was seen, as cases reported in literature [9]. Four cases of radiation induced acneiform eruption were seen. Few such cases have been reported in literature [10].

Conclusion

- The most common cutaneous manifestation seen in this study is grade 1 with 24 patients (48%) developing the reaction, followed by grade 2 in 18 patients (36%).
- Among the mucosal manifestations grade 1 was seen in 27 patients (54%) as the commonest.
- Pharynx and larynx involvement was seen in some of the patients in this study.
- Radiation dermatitis is one of the most common acute toxicities of both RT and CRT.

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