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Original Article

An audit of Grade III or more skin reactions in consecutively assessed patients at a modern radiation oncology center

ABSTRACT

Purpose: Radiation dermatitis is most common and debilitating side effects of radiotherapy leading to treatment interruption, thereby compromising the local control, and effecting quality of life. With the invent of modern imaging and recent advances in megavoltage radiotherapy, radiation-related side effects have reduced. In this audit, we report the risk factors associated with Grade III dermatitis in modern centers.

Materials and Methods: We analyzed 172 patients treated with volume modulated arc therapy (VMAT) and static field intensity-modulated radiotherapy (SFIMRT) at our center. All head and neck, breast, gynecological, GU malignancies, and sarcoma patients treated with a dose of >45 Gy from April 2018 to December 2019 were included in the study. On couch, treatment verification was done with cone-beam computer tomography (CBCT). Slice-by-slice verification of planning target volume (PTV) with CBCT was done in the first three fractions and weekly thereafter. Skin evaluation was done using CTCAE v. 5. Statistical analysis was done using SPSS v. 22.

Results: Of the 172 patients treated with VMAT and SFIMRT, 15 patients (8.7%) had Grade III dermatitis. Grade III dermatitis was mostly seen in breast cancer followed by head-and-neck patients. More reactions were observed in patients with advanced stage disease. Treatment verification is important at the later course of treatment, especially in head-and-neck cases where the treatment volume is large and PTV may extend outside skin. Contributing factors of radiation dermatitis at modern radiotherapy center are gene mutation, use of concurrent chemoradiotherapy, and bolus.

Conclusion: We hereby conclude that PTV mismatch in weekly treatment verification, genetic mutations, concurrent chemo-radiotherapy, use of thermoplastic mask, and bolus are the contributing factors for Grade III dermatitis in modern radiotherapy centers.

KEY WORDS: Planning target volume mismatch, radiation dermatitis, treatment verification

Vikas Kumar Pandey, Anusheel Munshi, Bidhu Kalyan Mohanti, Kanika Bansal, Khushboo Rastogi, Tharmarnadar Ganesh, Rohit Singh Chauhan, Bhavini Chaudhari, Pramod Pandey

Department of Radiation Oncology, Manipal Hospital Dwarka, Delhi, India

For correspondence: Dr. Vikas Kumar Pandey, Department of Radiation Oncology, Manipal Hospital, Dwarka, Delhi - 110 075, India. E-mail: kpvikas1104@gmail.com

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INTRODUCTION

Radiation dermatitis is one of the most common side effects of radiotherapy. In varying extent, it affects approximately 95% of the patients receiving radiotherapy with curative intent, especially in patients with skin, breast, head and neck, sarcoma, and pelvic malignancies.[1] Approximately 20%–45% of patients of head-and-neck cancers experience severe dermatitis in the form of moist desquamation and ulceration.[2] The incidence of moist desquamation was lower in breast cancer patients treated with intensity-modulated radiotherapy (IMRT) (31.2%) compared to 3-dimensional conformal radiotherapy (3DCRT) (47.8%).[3]

Mechanism of cell kill by radiotherapy involves ionization of cellular water and generation of free radicals; irreversible double-stranded DNA breaks, and inflammation.[4] Radiation dermatitis is deterministic effect (erythema after >2 Gy; dry desquamation after >12–20 Gy; moist desquamation after >20 Gy; and necrosis after >35 Gy). Repeated low-dose exposure to ionizing radiation prevents DNA and tissue repair.[5]

Radiation dermatitis may affect the patient's quality of life, resulting in a potentially detrimental cessation of therapy and diminished esthetic appeal.[6] Novel radiotherapy techniques such

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as IMRT and volume-modulated arc therapy (VMAT), along with advanced imaging and treatment schedules, have been partially being successful in reducing these side effects.[7]

In our department we reviewed, the first 172 patients treated with modern radiotherapy and assessed the patients who developed Grade III dermatitis. The aim of this audit is to report the factors leading to Grade III and higher dermatitis in patients treated at modern centers, and megavoltage linear accelerator (LINAC) based radiotherapy.

MATERIALS AND METHODS

We retrospectively identified 172 patients treated with modern radiotherapy at our hospital from April 2018 to December 2019, treated with a dose of more than 45 Gy by either static field IMRT (SFIMRT) or VMAT technique using 6 MV photon beam. On couch treatment, verification was done with cone-beam computer tomography (CBCT). CBCT was done during first three fractions and weekly thereafter. In this clinical audit, we reviewed all the patients who developed Grade III dermatitis during the course of treatment. All likely causative factors for skin reactions were recorded for each patient like matching planning target volume (PTV) during weekly treatment verification, genetic mutations, concurrent chemo-radiotherapy, use of thermoplastic mask, and bolus. PTV was trimmed 3 mm from skin surface in all patients as per institutional policy, except in radiotherapy to chest wall postmastectomy and in sarcoma patients. Modern megavoltage LINACs have skin-sparing effects. Based on institutional practice, we do not use any prophylactic cream. We treated patients with steroid creams and betadine lotion, postradiotherapy-induced Grade-III dermatitis.

Skin evaluation

All patients were reviewed weekly during treatment to record the incidence of acute radiation dermatitis using Common Terminology Criteria for adverse events version 5.0.[8] The grading of CTCAE v5.0 for acute dermatitis is shown in Table 1. We specifically assessed the importance of treatment verification with CBCT.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. IBM Corp. Released 2013.

RESULTS

Out of 172 patients treated at our center, 15 patients (8.7%) identified with Grade III dermatitis, and detailed clinical audit was done for these patients. Patient characteristics are shown in Table 2. Median overall age was 55.6 years, ranging from 40 to 68 years. Classification by tumor site revealed the most common site for Grade III dermatitis as head-and-neck region followed by breast. The most common histology was squamous cell carcinoma. Three patients were Stage II, five Stage III, and seven Stage IV. Most patients received adjuvant radiotherapy. One patient had ATM gene mutation.

All patients were treated with modern radiotherapy technique VMAT and SFIMRT. Possible factors contributing to grade 3 dermatitis is listed in Table 3. POCL thermoplastic mold used in 14 patients out of 15 patients with Grade III dermatitis. Bolus is used in one patient who had synovial sarcoma of forearm with recurrence at postoperative scar. Two re-irradiation patients developed severe dermatitis. All patients were treated with six MV photon beam. Total dose ranged from 45 Gy to 78 Gy. Out of 15 patients with Grade III dermatitis,13 patients received conventional fractionation, while two patients received hypofractionated radiotherapy. Grade III dermatitis was observed in seven of the 79 (8.9%) patients of head-and-neck cancer and 5 of the 35 (14.3%) patients who underwent breast irradiation. Concurrent chemotherapy was used in seven patients. Platinum-based chemotherapy was the most common concurrent chemotherapeutic agent used. Due to Grade III dermatitis, treatment was interrupted in five patients. On evaluation of weekly CBCT, it is seen that, in three cases, PTV margin was outside the skin, leading to Grade III reactions at the end of treatment [Figures 1 and 2].

Details of target volume and the site and volume of Grade III dermatitis are shown in Table 4. It was observed that most of the skin reactions were adjacent to the primary target volume. Most skin reactions were observed at the change in body contours that is either in lower neck and supraclavicular fossa (in case of head and neck cancers) and in axilla (in breast patient).

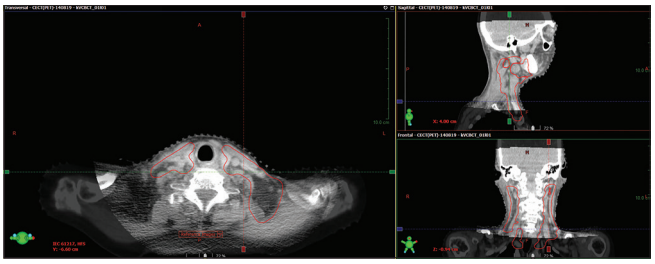


Figure 1: Initial cone beam computer tomography at time of first fraction

Table 1: CTCAE v5.0 for acute dermatitis

Adverse events	Grade I	Grade II	Grade III	Grade IV	Grade V
Radiation dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate erythema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

CTCAE=Common terminology criteria for adverse event

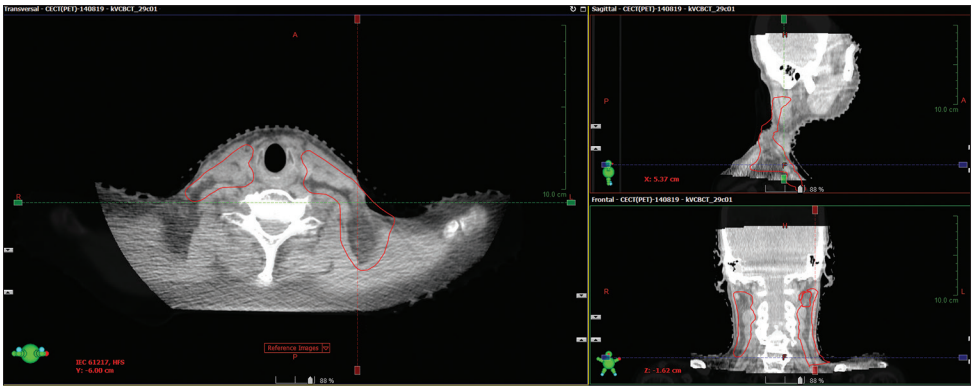


Figure 2: Cone beam computer tomography at 31st fraction of radiotherapy



Figure 3: Grade III skin reaction in one patient with carcinoma breast

The linear relationship between radiation dose changes and skin response is shown in Graph 1. It was observed that when we followed the conventional fractionation, the skin reactions were observed during treatment. The most of carcinoma breast patients were treated with hypofractionated regimen; Grade III dermatitis was observed postradiotherapy Figure 3. Grade I toxicity was observed after a cumulative dose range of 8–14 Gy, Grade II dermatitis was observed after a cumulative dose of 26–39 Gy, and Grade III toxicity was observed after cumulative dose of 36–65 Gy. The graph depicts that there is a wide spectrum for Grade III toxicity, which may be due to technical issues (dose, volume irradiated, and technique).

DISCUSSION

Radiation dermatitis can be acute or chronic. Acute dermatitis is one of the most common side effects of radiotherapy, developing within 90 days of starting radiation treatment.[4] Various etiological factors associated with radiation dermatitis include patient-related factors include genetic susceptibility and radiation dosing and schedule.

Different areas of body have variable sensitivity to radiation. Skin of anterior neck, extremities, chest, abdomen, and face are most sensitive.[9] In head-and-neck patients, most of the skin reactions were noted at anterior neck, especially in supraclavicular region. Even though the mask was fitting properly in the face, we noticed that this region tends to have most variation on weekly CBCT taken at the latter part of treatment (beyond 4 weeks). This finding calls for a careful matching of PTV with the reference image in the supraclavicular region during treatment verification, even when the mold is fitting properly or even if the PTV in the face and upper neck region has been matched. The supraclavicular region should be given importance during verification, as it might be the first site where PTV margins extend outside the skin and increased susceptibility of this region to radiation during the course of treatment as seen in most of

Table 2: Patient characteristics

Parameters	Grade III dermatitis (*n*=15)	Overall patients (*n*=172)
Age (years), median (range)	55.6 (40-68)	55 (-91)
Sex		
Male	6 (40)	100
Female	9 (60)	72
Site		
Head and neck	7 (46.7)	64
Breast	5 (33.3)	33
Extremity	1 (6.7)	4
Pelvis	2 (13.3)	55
Histology		
Invasive ductal carcinoma	5 (33.3)	28
Squamous cell carcinoma	8 (53.3)	57
Adenocarcinoma	1 (6.7)	28
Synovial sarcoma	1 (6.7)	3
TNM stage		
I	0	25
II	3 (20)	34
III	5 (33.3)	61
IV	7 (46.7)	52
Radiotherapy intent		
Neo-adjuvant	1 (6.7)	6
Adjuvant	10 (66.7)	58
Radical	4 (26.7)	108
Genetic mutations		
Present	1 (6.7) – ATM gene	1
Absent	14 (93.3)	171
Re-irradiation		
Yes	2 (13.3)	9
No	13 (86.7)	163

TNM=tumour node metastases

our patients. In our audit, three head-and-neck cancer patients with Grade III dermatitis had these reactions in supraclavicular region only, while other four patients of head-and-neck cancer patients had reactions in anterior neck along with supraclavicular region. Frequent CBCT should be taken for verification or a new adaptive plan should be considered for the patients during the course of radiation treatment.

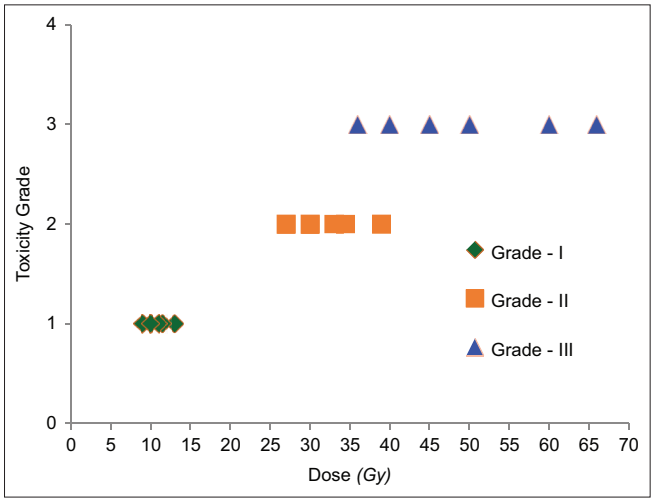
Novel radiation technique, IMRT and VMAT, delivers optimum dose to planned target volume and minimizing the dose to Organ At Risks (OARs) and thereby reducing skin toxicity. In our hospital, all patients receiving breast irradiation were planned with SFIMRT, and patient receiving radiation for head-and-neck cancers were planned with VMAT. Literature suggests that breast patients treated with SFIMRT have fewer moist desquamation compared to 3DCRT (31% vs. 48%).[3] Grade III dermatitis was observed in 5 of the 35 (14.3%) patients who underwent breast irradiation. All these patients were treated with SFIMRT technique. Three patients treated with hypofractionated radiotherapy to the breast developed radiation dermatitis after treatment. Both observational study and randomized studies have shown that hypofractionation is associated with less acute effects compared to conventional fractionation.[10] However, these studies did not ascertain the acute dermatitis after the completion of treatment.

Even though the thermoplastic mask used in head and neck cases provides good immobilization, it increases the surface dose, and the maximum dose is delivered at a shallower depth, thereby increasing skin toxicity.[11] Out of 15 patients

Table 3: Possible factors

Contributing factors	Number
Technique	
Volume modulated arc therapy	9 (60)
Static field intensity-modulated radiotherapy	6 (40)
Orfit used	
Yes	14 (93.3)
No	1 (6.7)
Bolus used	
Yes	1 (6.7)
No	14 (93.3)
Energy	
Volume modulated arc therapy-6x	9 (60)
Static field intensity-modulated radiothearapy-6x	6 (40)
Total dose (Gy)	
45-50	5
>50-60	6
>60-76	4
Dose per fraction	
1.8-2.2	13 (86.7)
2.3-2.6	2 (13.3)
Concurrent chemotherapy	
Yes	7 (46.7)
No	8 (53.3)
Chemotherapy agent	
Platinum based	5 (71.4)
Others	2 (28.6)
Gap due to skin reactions	
Yes	5 (33.3)
No	10 (66.7)
PTV outside skin during CBCT verification	
Yes	3
No	12

PTV=Planning target volume, CBCT=Cone-beam computer tomography



Graph 1: Relationship between dose and skin toxicity observed in patients

Table 4: Association of dose and Grade III dermatitis

Volume of target (PTV)	PTV from skin	Volume of Grade III dermatitis	Dose to site of Grade III dermatitis	Site of dermatitis	Relationship of volume and dermatitis
1643.5	0	11.4	45.52	Peri-anal region	Within field
1099	3	4.3	5.7	Right axilla	Within and adjacent
1125	3	3.6	19.14	Perianal region	Within and adjacent
797	3	2.8	32.87	Right axilla	Adjacent to high dose region
1109	0	1.7	40.7	Right forearm	Within high dose region
897.3	3	0.5	44.4	Right axilla	Adjacent to high dose region
475.5	0	0.9	32.98	Left axilla	Within high dose region
617	0	0.5	39.43	Right axilla	Adjacent to high dose region
1012	3	4.1	45.71	Bilateral SCF and lower neck	Adjacent to high dose region
179	3	3.9	43	Right SCF	Adjacent to high dose region
514	3	9.1	44.3	Right SCF and lower neck	Adjacent to high dose region
303	3	3.9	40.4	Right SCF and lower neck	Adjacent to high dose region
446	3	12.2	51.77	Bilateral SCF and lower neck	Adjacent to high dose region
336	3	15.2	47.47	Bilateral SCF and lower neck	Adjacent to high dose region
661	3	9.9	51.21	Left SCF and lower neck	Adjacent to high dose region

PTV=Planning target volume, SCF=Supraclavicular fossa

who developed Grade III reactions, thermoplastic mold was used in 14 patients. Even the batch-to-batch difference in the thermoplastic material can be a contributing factor. Several studies in literature suggest measures to decrease skin reactions. Penoncello and Ding[12] reported less skin toxicity with VMAT compared to IMRT, by reducing skin dose in all regions of the body. ICRU report 83[13] has proposed to crop PTV 3 mm from the body to prevent optimization issue in buildup regions during planning, except when skin is part of CTV (clinical target volume); the same was incorporated during planning in all our patients. Concurrent chemotherapy potentiates the effect of radiotherapy, thereby increasing cellular damage and hindering tissue repair. Giro *et al*.[14] reported greater skin toxicity was observed in patients treated with concurrent chemo-radiotherapy and recommended treatment interruption if Grade III dermatitis develops at a total dose <40 Gy. In our group, four patients treated with concurrent chemoradiation had treatment interruption due to Grade III dermatitis. Gap correction was applied for one patient whose gap was for 6 days. All patients who developed Grade III dermatitis were managed conservatively. IMRT and VMAT by default do not point to reduced skin dose. Although OAR doses are significantly controlled, we do not try to reduce the skin dose intentionally. In VMAT, since the beam entry points are distributed over a large area, skin dose might decrease. However, this advantage is partially offset by the increased oblique incidence of the beam, thereby losing the advantage.

ATM gene mutation and other hereditary diseases with impaired DNA repair capacity are associated with increased susceptibility to radiation.[7] In our study, one patient receiving postoperative hypofractionated radiotherapy for breast cancer, with ATM gene mutation had Grade III dermatitis.

The major limitation of our study is that it is a single institution study, and the number of patients may not be sufficient to draw statistically significant results. However, the study does point out the need for periodic audit in modern radiotherapy centers.

CONCLUSION

Nearly 8.7% of patients develop Grade III or more skin reactions even with most modern radiotherapy technology. Contributing factors include PTV mismatch in weekly treatment verification, genetic mutations, concurrent chemo-radiotherapy, use of thermoplastic mask, and bolus. Radiation technologists should be given special training for matching PTV and computed tomography images. Periodic audit, weekly patient review, and plan review with the radiation oncology can help minimize the side effects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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