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## Comparison of skin toxicity in 26 Gray x 5 Fractions vs 40 Gray x 15 Fractions in early-stage post operative Breast cancer

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### ABSTRACT

**Objective:** *To compare the effects between hypo fractionated and ultra hypo fractionated radiation treatment in early breast cancer.*

**Methods:** *Cross-sectional Comparative study was started after getting approval from the ethical review committee of the hospital, the study was conducted at the Department of RadiationOncology, Combined Military Hospital, Rawalpindi. Radiation induced skin changes were assessed periodically during treatment, post treatment and one month after treatment by history and local examination and degree of radiation dermatitis was categorized according to CTCAE.*

**Results:** *The mean age of patients was 55 in this study. Radiation dermatitis was significantly affected by the stage, type of surgery and volume of the tissue receiving more than 107& RT dose, however no statistical difference was noted amongst the hypo and ultra hypo fractionated regimen.*

**Conclusion:** *The study illustratedno significant skin toxicity observed in patients receiving hypo fractionatedor ultra hypo fractionated radiation treatment in early breast cancer.*

**Keywords:** *Breast cancer, hypo fractionated radiation, radiation dermatitis, whole breast irradiation, ultra hypo fractionated irradiation.*

## 1. INTRODUCTION

Breast cancer is the commonest malignancy in females.(1) Most of the patients are prescribed adjuvant radiation in either Ultra Hypo fractionated regimen or Hypo fractionated doses depending upon various criteria mentioned in standard guidelines(2). Comparing various radiotherapy prescriptions has been part of many trials in terms of locoregional failure, overall survival and late toxicity effects.(3)

Radiation dermatitis is one of the most frequent side effects in breast cancer patients undergoing adjuvant whole-breast or chest wall irradiation (4). It has been observed in the whole Breast irradiation as well as post Mastectomy chest wall irradiation. Frequency and severity of acute radiation-induced skin reactions during Ultra Hypo fractionated vs. Hypo fractionated regimen varies among patients(4).

Both hypo fractionated and ultra hypo fractionated radiation therapy are adopted at our institute as per international guidelines. In this study, conducted at our institute 60 patients were analyzed for skin toxicity along with various clinical and dosimetric parameters leading to skin toxicity.(2)(5)

## 2. METHODOLOGY

After getting approval from the ethical review committee of the hospital, the study was conducted at the Department of Radiation Oncology, Combined Military Hospital, Rawalpindi. Radiation induced skin changes were assessed periodically during treatment, post treatment and one month after treatment by history and local examination and degree of radiation dermatitis was categorized according to CTCAE.

We selected 67 patients diagnosed with early breast cancer, 29

were treated with WLE and 38 patients were treated with Modified Radical Mastectomy. Inclusion criteria were Age: > 18 years and <85 years, Histopathology: Invasive mammary carcinoma and Invasive Ductal carcinoma irrespective of receptor status, Early-stage disease including stage I and stage II, breast conserving surgery receiving 26 GY in 5 Fractions and 40 GY in 15 fractions given to patients receiving Modified Radical Mastectomy. Exclusion criteria were Pregnancy, previous thoracic irradiation, metastatic disease, ductal carcinoma in situ, previous operation in irradiated area, active dermatitis in the irradiated region and refusal of the patient to participate in the study.

After detailed evaluation of the patients planning simulation scan was performed on CT simulator. The area scanned was from Mastoid process cranially and upper abdomen caudally. Patients were in supine position on breast board inclined at 15 degrees with both the arms above head and supported on a T bar. The scan was done with slice thickness of 3mm. Following 3D conformal planning and tangential beam arrangement 6MV photon energy was used. All patients were treated by Varian LINAC. Left side tumors were treated with Deep inspiratory breath holding technique. International commission on radiation units and measurements with dose limits of 95-107%. Skin care was explained in detail to all the patients and those experiencing skin toxicity Grade 2 were give 1% silver sulphadiazine for local application as per our institution practice.

After checking the reliability from the reliability test in SPSS which came out to be 0.331 shows that there exist internal consistency and reliability. The reliability coefficient normally ranges between 0 to 1. After finding reliability, the independent variables: age, stage, type of surgery, grade of toxicity, bolus and volume receiving, and dependent variable Skin Toxicity are analyzed using Kruskal

Wallis test with grouping variable skin toxicity. The skin toxicity treatment of 26 Gray in 5 fractions and 40 Gray in 15 fractions were selected for the analysis so out of 67 cases, 57 cases (patients) were selected based on the objective of the study.

### 3. RESULTS

The study was conducted in CMH Rawalpindi for the duration of two years after approval from the ethical review committee. The study enrolled 67 patients who were diagnosed with breast cancer and met the inclusion and exclusion criteria as per study design. The median age of the patients was 55 years (Range 26-85 years). The study includes three stages of breast cancer with 7.5% being stage I, 67.2% were stage II and approximately 25% were stage III patients. 38 patients underwent MRM, and 29 patients had wide local excision of the primary tumor. The patients were categorized in two fractionation groups i.e hypo fractionated (37 patients) and ultra hypo fractionated (20 patients) regimen.

A total of 10 patients were excluded because of the difference in radiation dose due to the radiation boost given to the tumor bed in breast conservative surgery. Most patients were diagnosed with invasive ductal carcinoma. MRM. Most of the patients had received neoadjuvant chemotherapy. Patients were treated by 3D conformal radiotherapy technique. The patients were followed in OPD clinics in week 1, 2 and 4 weeks after completion of radiotherapy to assess the radiation induced dermatitis. 58 patients had Grade 1, 7 patients had Grade 2 and only 2 had Grade 3 skin changes. None of the patients showed clinical features of ulceration. The end point of the study was to compare different grades of skin toxicity in breast cancer patients who underwent WLE and MRM and received hypo and ultra hypo fractionated radiotherapy regimen. It was found that

radiation dermatitis was significantly affected by the stage, type of surgery and volume of the tissue receiving more than 107% RT dose, however no statistical difference was noted amongst the hypo and ultra hypo fractionated regimen.

**Table 1: Mean Ranks Calculation in Kruskal Wallis Test**

| Ranks                |         |    |           |
|----------------------|---------|----|-----------|
|                      | RT Dose | N  | Mean Rank |
| Age                  | 26      | 20 | 31.98     |
|                      | 40      | 37 | 27.39     |
|                      | Total   | 57 |           |
| Stage                | 26      | 20 | 22.70     |
|                      | 40      | 37 | 32.41     |
|                      | Total   | 57 |           |
| Type of surgery      | 26      | 20 | 19.05     |
|                      | 40      | 37 | 34.38     |
|                      | Total   | 57 |           |
| Grade of toxicity    | 26      | 20 | 27.38     |
|                      | 40      | 37 | 29.88     |
|                      | Total   | 57 |           |
| Bolus                | 26      | 20 | 25.43     |
|                      | 40      | 37 | 30.93     |
|                      | Total   | 57 |           |
| Vol receiving >107 % | 26      | 20 | 22.90     |
|                      | 40      | 37 | 32.30     |
|                      | Total   | 57 |           |

**Table 2: Test Statistics**

| Test Statistics <sup>a,b</sup>      |      |       |                 |                   |       |                     |
|-------------------------------------|------|-------|-----------------|-------------------|-------|---------------------|
| 6                                   | age  | Stage | Type of surgery | Grade of toxicity | Bolus | Vol receiving >107% |
| Chi-Square                          | .992 | 6.341 | 16.199          | 1.042             | 3.293 | 4.161               |
| Df                                  | 1    | 1     | 1               | 1                 | 1     | 1                   |
| Asymp. Sig.                         | .319 | .012  | .000            | .307              | .070  | .041                |
| a. Kruskal Wallis Test              |      |       |                 |                   |       |                     |
| b. Grouping Variable: Skin Toxicity |      |       |                 |                   |       |                     |

#### 4. DISCUSSION

Breast cancer is one of the commonest causes of malignancy in females across the world. The management of breast cancer is dependent upon many factors, but the most crucial factor is the stage of the patient. In early-stage disease Radiotherapy is the cornerstone of the treatment. Different dose fractionation regimens are used in patients. In Conventional fractionated regimen 40 Gray in 15 fractions is used in patients undergoing mastectomy and in ultra hypo fractionated regimen 26 Gray in 5 Fractions is used in patients mostly undergoing breast conserving surgery. Radiation induced skin changes were reported by almost all the patients in the study.

Skin covers the entire external surface of the body.(9)(10). It consists of two layers, the outermost is the Epidermis, and the deeper layer is Dermis, which is resting on subcutaneous fatty layer, the panniculus adiposus. The epidermis contains melanocytes, Langerhans cell histiocytes and Merkel cells and the dermis contains collagen. Elastic fibers. Blood vessels. Nerve endings and fibroblasts.

Radiation dermatitis is one of the most common adverse effects of Radiotherapy and occurs in approximately 90% of patients receiving ionizing radiation. (11)(12). These adverse events can be acute or chronic. Basal keratinocytes, stem cells in hair follicles and melanocytes are extremely radiosensitive. Acute Radiation dermatitis is defined as symptoms within 90 days of radiation and late events are defined as events occurring after 90 days. Acute effects are due to ionization of cellular water and generation of free radicals lead to irreversible double-stranded breaks in nuclear and mitochondrial deoxyribonucleic acid (DNA) causing inflammation. Hallmark of radiation induced dermatitis is trans endothelial migration of leucocytes and other

inflammatory markers from circulation to the region receiving radiation. The destruction of a large proportion of basal keratinocytes results in the disruption of the self-renewing property of the epidermis. Acute effects have been correlated with increased formation of various cytokines and chemokines, in particular interleukin (IL) 1-alpha, IL-1-beta, tumor necrosis factor (TNF)-alpha, IL-6, IL-8, chemokine ligand 4 (CCL4), cysteine-X-cysteine motif chemokine ligand 10 (CXCL10), and chemokine ligand. Ionizing radiation also causes degranulation of mast cells. In the late effects levels of Transforming growth factor beta is increased which leads to the signs and symptoms related to late cutaneous effects.(13)(14)

Several risk factors have also been associated with development of radiation dermatitis for example sun exposure, Staphylococcus decolonization, breast reconstruction and implants, obesity, and certain inherited skin disorders with increased susceptibility to development of radiation dermatitis.(15)

Patients are usually presented with clinical features of erythema, edema. Pigment changes dry desquamation and moist desquamation. During a fractionated course of 2 Gy per fraction of radiation therapy, erythema occurs at doses of 12 to 20 Gy, dry desquamation occurs at doses  $\geq 20$  Gy, and moist desquamation occurs at doses  $>50$  Gy or higher. The severity of radiation dermatitis can be assessed by several grading systems. The most used are the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria.

Many studies have been conducted in the past to observe the effects of radiotherapy on skin in breast cancer patients who received hypo fractionated or

ultra hypo fractionated radiotherapy regimen. (16)

A large mono institutional retrospective study was conducted by Anderi Fodor from 2009 to 2017 in which late skin effects were assessed in patients receiving hypo fractionated radiotherapy 40G/15F to whole breast. Acute and Late toxicity effects were observed. Median follow up was 72.4 months. (17)69% of patients observed Grade 1 toxicity, 14.3% in G2 and 1.7% in G3. Chemotherapy, obesity, use of bolus and planning target volume were associated with higher acute toxicity. In our study we had seen the association of stage, type of surgery and percentage of target volume being associated with higher incidence of radiation dermatitis although we had limitation of a smaller number of patients and limited time to complete the study.

A large prospective multicentre study was conducted between 2016 and 2022 by Marie Braund et al which compared acute skin toxicity events in conventional vs hypo fractionated radiotherapy in breast cancer patients receiving regional lymph node irradiation. In this study a total of 1727 patients were assessed. 82.2% of patients received conventional radiotherapy while 17.8% received hypo fractionated regimen. Incidence of grade 2 or above skin toxicity was lower in hypo fractionated arm. Odds ratio 0.34. The skin toxicity was seen mostly in the group who were planned with 3D conformal or IMRT plans. (18)

A multicentre study was conducted by Leonard Cristopher Schmel from 2017 to 2019 in which acute radiation dermatitis was assessed in breast cancer patients who received either conventional radiotherapy regimen of 50 G/25 F or hypo fractionated regimen of 40.05 G/15F. A total of 140 patients were enrolled and the assessed. Maximum radiation dermatological effects were

observed. (4)The results showed significantly lower rates of radiation dermatitis in hypo fractionated arm as compared to conventional Radiotherapy dose. In our study we compared the grades of radiation dermatitis in two groups i-e hypo fractionated and ultra hypo fractionated therapy. We had limitation of a smaller number of patients and the skin changes were assessed by clinical examination as compared to this study in which photo spectrometric skin readings were taken.

## 5. CONCLUSION

The study illustrated no significant skin toxicity observed in patients receiving hypo fractionated or ultra hypo fractionated radiation treatment in early breast cancer.

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