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IMPACT OF CHRONOMODULATED RADIOTHERAPY ON ACUTE SKIN TOXICITY IN CHEST WALL IRRADIATED BREAST CANCER PATIENTS – A SINGLE INSTITUTION ANALYSIS.

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Abstract: We explored the possible association between the timing of delivery of radiation and the grade of skin reaction that develops in breast cancer patients receiving chest wall irradiation as adjuvant treatment after modified radical mastectomy. Invasive breast cancer patients, registered during the period of January 2013 - December 2014, who had undergone modified radical mastectomy followed by chest wall irradiation, were eligible for inclusion to the study. All the patients received chest wall external beam radiotherapy (EBRT) to a dose of 50 Gy in 25 fractions, one fraction a day, five days a week, delivered as tangential opposed pair, from a Cobalt 60 teletherapy source. Patients were stratified based on whether they received EBRT in the morning (between 8 am – 11 am) or in the evening between (5 pm – 8 pm). The clinicopathological characteristics of patients in both the arms were relatively well balanced.

The incidence of higher grade of skin reaction (grade 3 or 4) was 22.5 % compared to 35.7 % in the morning and evening arms respectively, which was statistically significant (p = 0.039). The time to development of Grade 3 or 4 toxicity was 4.44 weeks compared to 4.11 weeks in the morning and evening arms respectively, suggesting that higher toxicity developed earlier in the patients receiving EBRT in the evening, though not statistically significant (p = 0.29).

INTRODUCTION

Breast cancer is currently the second most common cancer in Indian women with cervical cancer ahead in the list. But data predicts breast cancer to supersede cervical malignancy as the most common cancer in the near future. [1] Adjuvant irradiation of the chest wall and regional lymphatics is an integral part of the planned treatment protocol in a majority of the breast cancer patients. Radiation skin reactions are, to some extent, an inevitable consequence of radical radiotherapy. The development of skin reactions and its relation to the timing of radiation in breast cancer is the concern of this study, as has also been previously studied by Noh et al. [2]

The biological processes occurring in a living organism are basically controlled by a circadian rhythm adjusted to a round-the-clock 24 hour cycle. These endogenous rhythms are genetically fixed and they coordinate most of the significant biological activities happening in an individual, like sleep, secretions of hormones and metabolism etc. [3-5]

This circadian rhythm is genetically maintained amongst species and in humans it is controlled by the suprachiasmatic nuclei of the hypothalamus. The presence of several molecular clock genes has been already identified, that are involved in a feedback loop mechanism to control the rhythm. [3-5]

Bjarnason et al described the presence of a rhythmicity in the expression of these clock genes which regulate important transition points in the cell cycle, like the *MYC* (G0/G1 transition), *cyclin D1* (G1/S transition) and the *WEE1* (G2/M transition). [6]

Utilizing this concept of rhythmicity various therapeutic approaches have been examined in the past. This so called '**Chronotherapy**' and its impact in improving therapeutic efficacy has been extensively studied in animal models and verified in cancer treatment with significant success. [7-9]

In our department we have three shifts of radiation treatment due to the high patient load and about half of the patients receive radiation either during the morning hours (8am -11am) or during the evening hours (5pm-8pm). We investigated the relation between timing of radiation and the severity of skin toxicity developed as well as the mean time to development of the highest grade of toxicity.

MATERIALS AND METHODS

In our institution, 436 histopathologically proven breast cancer patients underwent modified radical mastectomy during the period from Jan 2013 to December 2014. Of these, 408 patients received radiation to the chest wall and regional lymphatics. In our retrospective study, we initially included the data of 230 patients who had received EBRT either in the morning (8 to 11 am) or in the evening (5 to 8 pm), for analysis. Later, we excluded patients who had metastatic disease (n=20), interruptions in their planned treatment schedule due to personal issues (n=39) and those with missing information relevant to the study (n=28). Finally, 143 patients were eligible for the data analysis. The study design and protocol was approved by the institutional review board and ethical committee.

All 143 patients had received chest wall irradiation using tangential opposed field technique, to a dose of 50 Gy in 25 fractions, one fraction a day, five days a week, for five weeks. Radiation was delivered by a Cobalt 60 teletherapy machine. The field borders used was as follows; superiorly the head of the clavicle, inferiorly 2 cm below the contralateral inframammary fold, medially the midline and laterally the midaxillary line. All the patients received radiation to the supraclavicular fossa to the same dose as per the above mentioned schedule.

All patients who had undergone radiation treatment were followed up on a weekly basis to observe for development of radiation induced skin reactions, as per our institutional protocol. The acute skin toxicity was reported and graded according to the Radiation Therapy Oncology Group (RTOG) criteria. Highest grade toxicity/ reaction over the period of treatment and time to develop skin reaction were noted. All these data were taken from the master file of the enrolled patients for the purpose of the study.

All statistical analysis were done using SPSS software version 18.0 and the variables were analyzed using descriptive analysis method.

Comparison of acute skin toxicity between the groups was done using independent t-test or Chi square test whichever was applicable. p-value of <0.05 was considered significant.

RESULTS

Of the 143 patients eligible for analysis, 49.6 % received radiation in the morning EBRT arm (n= 71) and 50.4% patients in the evening EBRT arm (n=72). The pretreatment characteristics were balanced between the two treatment arms (**Table 1**). Mean age was 50.3 years and 50.52 years for the morning arm and the evening arm respectively.

TABLE 1: PATIENT CHARACTERISTICS

VARIABLES		MORNING RT (N= 71) (8 to 11 am)	EVENING RT (N=72) (5 to 8 pm)
MEAN AGE (in years)		50.30	50.52
SEX	**MALE**	02 (02.8%)	01 (01.3%)
	FEMALE	69 (97.2%)	71 (98.7%)
LATERALITY	**RIGHT**	42 (59.1%)	41 (56.9%)
	LEFT	29 (40.9%)	31 (43.1%)
T-STATUS	**T1**	05 (07.0%)	07 (09.8%)
	T2	29 (40.8%)	28 (38.9%)
	T3	28 (39.5%)	29 (40.2%)
	T4	09 (12.7%)	08 (11.1%)
N-STATUS	**N0**	04 (05.6%)	03 (04.1%)
	N1	36 (50.7%)	38 (52.9%)
	N2	27 (38.0%)	28 (38.9%)
	N3	04 (05.7%)	03 (04.1%)
ER- STATUS	**POSITIVE**	43 (60.5%)	42 (58.3%)
	NEGATIVE	28 (39.5%)	30 (41.7%)
PR- STATUS	**POSITIVE**	44 (61.9%)	38 (52.9%)
	NEGATIVE	27 (38.1%)	34 (47.1%)
HER 2 neu	**POSITIVE**	16 (22.5%)	15 (20.8%)
	NEGATIVE	55 (77.5%)	57 (79.2%)
CHEMOTHERAPY	**NEOADJUVANT**	32 (45.1%)	35 (48.6%)
	ADJUVANT	39 (54.9%)	37 (51.4%)
ECOG	**0**	64 (90.1%)	70 (97.2%)
	1	07 (09.9%)	02 (02.8%)

All patients received chemotherapy either as neoadjuvant or adjuvant therapy. While 86.7 % of the patients (n=124) received adjuvant endocrine therapy, 21.6% (n=31) received biological therapy with Trastuzumab.

When the incidence of acute skin toxicity was analyzed, overall 28.6 % of patients (41/143) developed severe (RTOG Grade 3 or 4) toxicity, with 22.5 % of patients (16/71) in the morning arm compared to 34.7 % patients (25/72) in the evening RT arm, which was statistically significant (**p=0.039**). Thus, significantly higher incidence of skin reactions was noticed in the patients receiving

RT in the evening hours (**Graph 1, Table 2**).

Graph 1

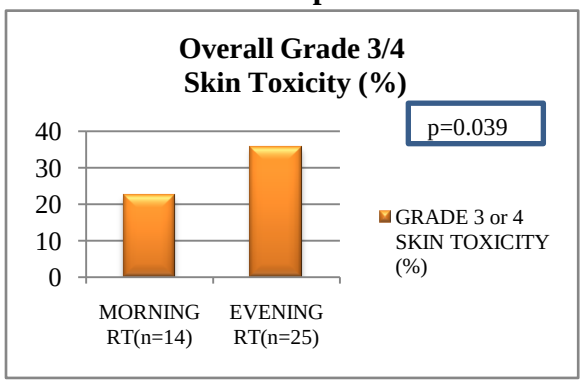
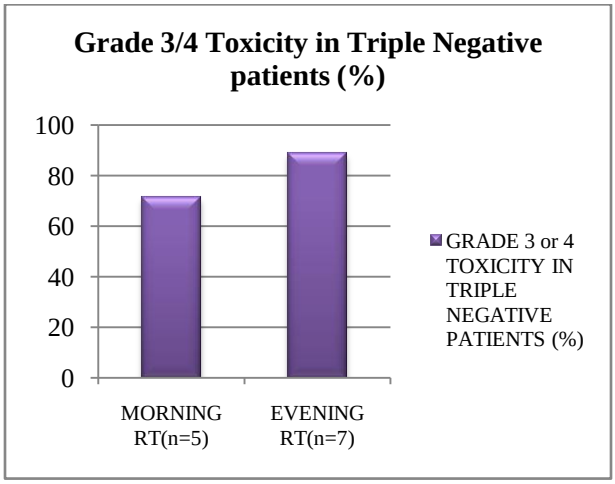


TABLE 2: ACUTE SKIN TOXICITY

VARIABLES	MORNING RT (N=71) (8 to 11 am)	EVENING RT (N=72) (5 to 8 pm)
GRADE OF TOXICITY		
GRADE 1	20 (28.2%)	09 (12.5%)
GRADE 2	35 (49.3%)	38 (52.8%)
GRADE 3	16 (22.5%)	24 (33.3%)
GRADE 4	0 (0.0%)	01 (01.4%)
GRADE 3 & 4 TOXICITY COMBINED	16 (22.5%)	25 (34.7%)
MEAN TIME TO DEVELOP GRADE 3/4 TOXICITY (IN WEEKS)	4.44	4.11

On multivariate analysis, there was no pathological variable responsible for the increased propensity for severe skin reactions in the evening RT arm. But, interestingly in the small subset of triple negative patients (n=16) there was an increase in the frequency of severe toxicity compared to the other receptor positive population. This higher rate of Grade 3/ 4 toxicity with triple negative patients was seen in both the arms, with 5 out of 7 patients (71.4%) in the morning arm and 8 out of 9 (88.9%) in the evening arm (**Graph 2**).

Graph 2



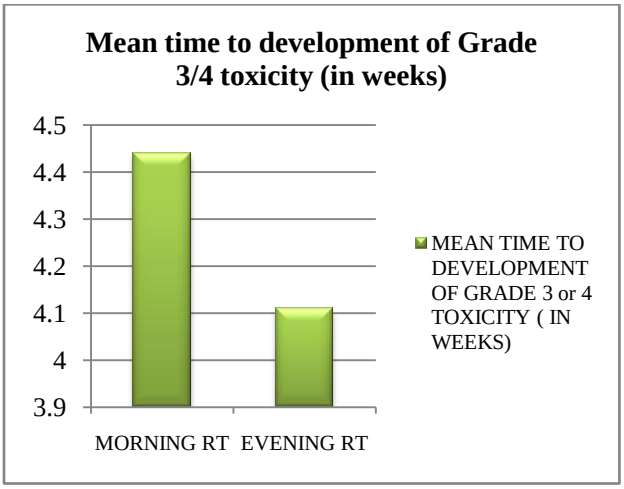
One triple negative patient in the evening arm had to undergo treatment interruption after 21 fractions due to Grade 4 skin reaction in the form of hemorrhage. She recovered with supportive care and completed her radiation treatment (**Table 3**).

TABLE 3: SUBSET ANALYSIS BASED ON RECEPTOR STATUS

VARIABLES	MORNING RT (8 to 11 am)	EVENING RT (5 to 8 pm)
HORMONE POSITIVE		
GRADE 1&2	55 (77.5%)	47 (65.3%)
GRADE 3&4	09 (12.7%)	16 (22.2%)
TRIPLE NEGATIVE		
GRADE 1&2	02 (28.6%)	01 (11.1%)
GRADE 3&4	05 (71.4%)	08 (88.9%)

The mean time to development of the highest grade of toxicity was shorter in the evening arm (4.11 weeks) compared to the morning RT arm (4.44 weeks) (p=0.29) (**Table 2, Graph 3**).

Graph 3



We found no difference in degree of development of skin reactions correlating to whether the patient had received neoadjuvant or adjuvant chemotherapy (**Table 4**).

TABLE 4: SUBSET ANALYSIS BASED ON NEOADJUVANT/ADJUVANT CHEMOTHERAPY

VARIABLES	MORNING RT (8 to 11 am)	EVENING RT (5 to 8 pm)
NEOADJUVANT		
GRADE 1&2	25 (35.2%)	22 (30.5%)
GRADE 3&4	07 (09.8%)	13 (18.1%)
ADJUVANT		
GRADE 1&2	30 (42.3%)	25 (34.7%)
GRADE 3&4	09 (12.6%)	12 (16.7%)

DISCUSSION

In the present study, we assessed whether there is any difference in the incidence of higher grade of skin toxicity with respect to the timing of delivery of radiation. The total incidence of Grade 3 or 4 skin reaction in total was 28.6 %. This value was in correspondence with the results of other published randomized trials that compared standard tangential techniques with newer modalities like intensity modulated radiation therapy.[10] With regards to the two arms, the morning RT arm head a significantly lower incidence of Grade 3 or 4 acute skin reactions.

The plausible explanation to the decreased prevalence of acute skin toxicity in the morning could be due to the fact that those cells were in the relatively radioresistant G1 phase, when compared to the evening RT arm. In the evening, the cells would be more in the radiosensitive G2 phase of the cell cycle. [11]

In the subset of triple negative patients , the higher incidence of severe skin toxicity irrespective of the treatment time might probably due to the deficient DNA repair mechanism, related to the increased chance of harboring a BRCA mutation. Increase in radiosensitivity with BRCA mutation has been earlier observed. [12-13] This concept needs to be studied in greater detail to be validated.

Chauhan et al in a review have exhaustively elaborated the molecular mechanism, the significance of the circadian rhythm and how it is linked to the DNA repair mechanism. [14]

Bjarnason et al have studied the nuclear expression of cell cycle proteins by immunohistochemistry as a function of the time of day in oral mucosa biopsies from healthy male human volunteers. A significant circadian rhythm was found for all studied proteins, with the high point of expression for p27 at 6:00 AM (early G1-phase marker), p53 at 10:50 AM (late G1-phase marker), cyclin-E at 2:50 PM (S-phase marker), cyclin-A at 4:00 PM (G2-phase marker), and cyclin-B1 at 9:10 PM (M-phase marker). [6]

Bjarnason et al also demonstrated the beneficial effect of morning radiotherapy in head and neck malignancies with regards to reducing the severity of mucositis substantiating the circadian rhythm of cell cycle regulatory proteins.[15] Bashir et al had similar results demonstrating the efficacy of morning radiotherapy in decreasing mucositis in head and neck cancer. [8]

Shukla et al have demonstrated decrease in incidence of diarrhea in cervical cancer patients for whom radiation was delivered in the morning, suggesting the presence of a circadian rhythm to the cell cycle of the intestinal mucosal cells. [9]

There are randomized trials in other sub-sites as well, where a therapeutic advantage with chemotherapy delivered utilizing the circadian rhythm has been displayed; some commenting on skin and mucosal reactions too. [7, 16, 17]

CONCLUSION

There is definite and ample clinical evidence exploring the beneficial effect of chronomodulated radiotherapy in terms of decreasing normal tissue toxicity as well as improving therapeutic efficacy. But this phenomenon is yet to be implemented into routine clinical practice. Our study, though retrospective, has brought to light the beneficial effects of morning radiotherapy in decreasing radiation induced skin toxicity. Till other novel approaches for skin toxicity reduction come into existence, the concept of circadian variation and the beneficial effect of morning radiotherapy may be utilized. This is cost effective, simple and feasible beyond doubts.

CONFLICTS OF INTEREST: None

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