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Comparative Evaluation of Hypofractionated and Conventional Fractionated Radiotherapy in Post Mastectomy Carcinoma Breast Patients

Authors
Dr Roshani Vyas[1*], Dr Ashok Chauhan[2], Dr Paramjeet Kaur[3], Dr Joydeep Singh Vasant[4], Dr Jyoti Pannu[5], Dr Shashank Joshi[6], Dr Anil Khurana[7]
[1,4,5,6,7]Junior Resident, [2]Senior Professor, [3]Professor
PGIMS, Rohtak, India

Abstract
Purpose: *To compare the radiation induced toxicity and loco regional recurrence rates along with tolerability of hypofractionated radiation therapy with conventional fractionation radiation therapy in post modified radical mastectomy carcinoma breast patients.*
Material and Methods: *Sixty post modified radical mastectomised, histopathologically proven patients of breast carcinoma from October 2016 to October 2017.Group I patients received 42.7Gy/16Fr/3.1 weeks and Group II patients received 50Gy/25Fr/5weeks. Radiation induced toxicities were assessed using RTOG and WHO criteria each week during treatment & fortnightly for 1st month after treatment & also up to 6 months after treatment.*
Results: *A total of 60 (30 in each group) patients completed treatment and 6 months follow-up. At the end of treatment grade I skin reactions were seen in 15(50%) patients of group I and 9 (30%) patients of Group II, Grade II in 10(33.3%) patients of Group I and 9(30%) patients in group II, Grade III in 1(3.3%) patients of group I and 0 patients of group II, no Grade IV reactions in any patients. Grade I esophageal reaction was seen in 10(33.3%) patients in both the groups, Grade II in 3(10%) patients of Group I and 0 patients of Group II, no patient in Group II. Nausea and vomiting (WHO TOXICITY CRITERIA) Grade I was seen in 16(53.3%) patients of Group I and 13(43.3%) patients of Group II, Grade II in 3(10%) patients of Group I and 1(3.3%) of Group II. Local recurrence along with distant metastasis was noted in 5 patients of Group I and distant metastasis only in 5 patients of Group II at median follow up of 14 months.*
Conclusion: *Radiation induced acute toxicity was more in group I (hypofractionation group) as compared to group II (Conventional fractionation group) while late toxicity was similar in both groups, thus making it equally tolerable schedule. Whereas compliance was better in group I due to shorter duration of treatment. Local recurrence was noted in hypofractionation group (I) patients and not in conventional group (II). Distant metastasis occurrence was equal in both the groups at median follow up of 14 months after treatment.*

Introduction

In India, carcinoma breast often remains undetected until it has progressed to advanced stages. Due to lack of awareness, socioeconomic constraints, gender bias against females & illiteracy, patients report to the hospitals late,

when the disease has progressed & disseminated locally to stages III & IV. Thus they have to undergo mastectomy unlike lumpectomy for early stages, rendering mastectomy to be a common procedure in India still. Mastectomy followed by radiotherapy has been proven to significantly improve overall survival along with disease-free survival since decades now by various series and randomized controlled trials & is an established standard of treatment. Adding up to the economic, psychological & social burden to the patient with the added disadvantage of increased patient load & treatment cost on the treating institutions. The advent of hypofractionation in radiotherapy, has emerged as the most promising boon for patients of carcinoma breast. Here the patients receive more than 2Gy per fraction per day dose reducing the total dose & number of fractions needed for curative intent with a drastic reduction in the overall treatment time inturn increasing compliance. Hence a hypofractionation schedule was imbibed in the present study for its comparison with the conventional fractionation regime on the basis of tolerance, loco regional recurrence rates & compliance amongst the two groups.

Patients & Methods

Patient characteristic & pre-treatment evaluation

Sixty post modified radical mastectomised, radiotherapy naïve, histopathologically proven patients of breast carcinoma from October 2016 to October 2017 comprised sample for this study. The assessment of patient's general condition was done using Karnofsky Performance Status. Hematological assessment was done by a complete hemogram including hemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count and peripheral blood film. Biochemical assessment to assess the kidney and liver functions was done by the estimation of blood urea, serum creatinine, SGOT, SGPT levels, serum alkaline phosphatase levels. Chest X-ray and ultrasound of abdomen and pelvis was done in all patients. All patients were staged according to the criteria American Joint Committee on Cancer 7th edition. Patient characteristics are given in table -1.

Inclusion criteria

1. All histopathologically proven carcinoma breast patients, stage II and III who have undergone modified radical mastectomy.
2. Radiotherapy naïve patients.
3. Karnofsky status more than 70 Normal hemogram, liver function tests, kidney function tests and urine examination, with Hb>9 gm%, TLC>4x10^3/ml, platelets >1x10^5/ml, blood urea<40mg%, serum creatinine <1.7mg%, SGOT/SGPT<40 IU and serum alkaline phosphatase<13 KAU.
4. Patients who have signed the informed consent.

Exclusion criteria

The exclusion criteria for the study were

1. Patients having primary tumor less than 5 cm in size having no lymphatic or vascular invasion with free resection margins.
2. Patients having no positive lymph node, not fixed to one another or other structures, when at least 12 nodes has been examined histopathologically.
3. Patients who have received surgical treatment other than modified radical mastectomy.
4. Patients who have received radiation therapy elsewhere before being entered into the study.
5. Patients having inoperable disease at presentation.
6. Patients having distant metastasis at presentation.

Methodology

Patients were divided into 2 groups of 30 patients each by internet service website www.random.org/lists. Group I comprised randomly selected 30 patients receiving external radiation to chest wall and drainage areas, with a dose of 42.72Gy/16 fractions/3.1 weeks, 2.67 Gy per

fraction in a 5 days a week schedule. Group II comprised randomly selected 30 patients receiving external radiation to chest wall and drainage areas, with a dose of 50 Gy/25 fractions/5 weeks, 2 Gy per fraction in a 5 days a week schedule.

All patients were treated by ^{60}Co teletherapy machine by medial and lateral tangential fields to chest wall and lower axilla. And by direct anterior field to supraclavicular fossa and upper axilla with patient in supine position using standard breast board.

Assessment during treatment & in follow up period

Radiation effects on primary sites, lymph node drainage areas and irradiated normal tissue were carefully recorded. Acute toxicities noted were: cutaneous reactions, esophagitis, nausea and vomiting, according to WHO TOXICITY CRITERIA and RTOG CRITERIA. All the patients were followed up fortnightly during first followed by monthly up to 6 months. At each follow up patients were assessed for radiation-induced skin reactions, nausea/vomiting, difficulty in swallowing, shoulder movement restriction, difficulty in breathing, chest pain/angina, and graded according to WHO & RTOG criteria. Chest wall and lymph node drainage areas were carefully examined for local recurrence and systemic examination for distant metastasis.

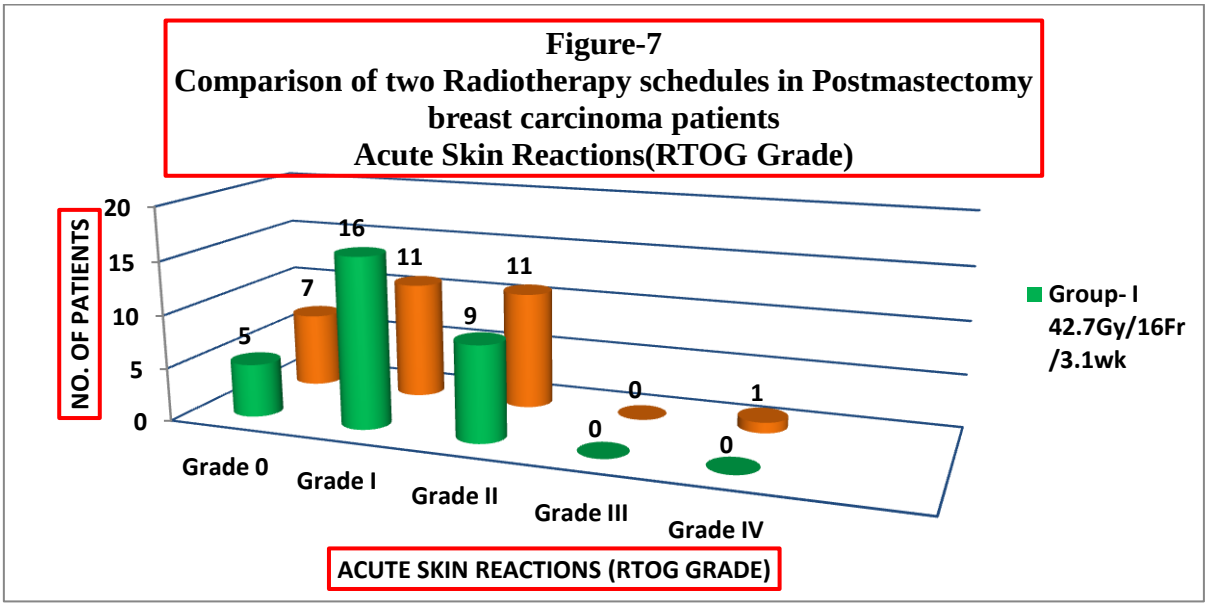
Results

Table 1 Patient Characteristics

Patient characteristics		Group- I 42.7Gy/16Fr/3.1wk (n=30)		Group II 50Gy/25Fr/5wk (n=30)		p value
		Number	(%)	Number	(%)	
Age Group(years)	≤ 40	8	26.7%	8	26.7%	1.00
	>40	22	73.3%	22	73.3%	
	Range	29-70		28-77		
	Median	63		55		
Background	Rural	20	66.7%	19	63.3%	0.787
	Urban	10	33.3%	11	36.7%	
Menstrual history	Pre menopausal	12	40%	13	43.3%	0.793
	Post menopausal	18	60%	17	56.7%	
Symptoms	Painless Lump in breast	27	90%	2790%		1.00
	Lump & bleeding/discharge from nipple	2	6.7%	13.3%		0.554
	Painful Lump	0		26.7%		0.150
	Pain only	13.3%		0		0.313
Duration of symptoms	≤ 1 month	0		0		NA
	1-6 months	1446.7%		23	76.7%	0.017
	>6 months	1653.3%		7	23.3%	0.017
Karnofsky Performance status (KPS)	80	10	33.3%	20	66.7%	0.010
	90	20	66.7%	10	33.3%	0.010

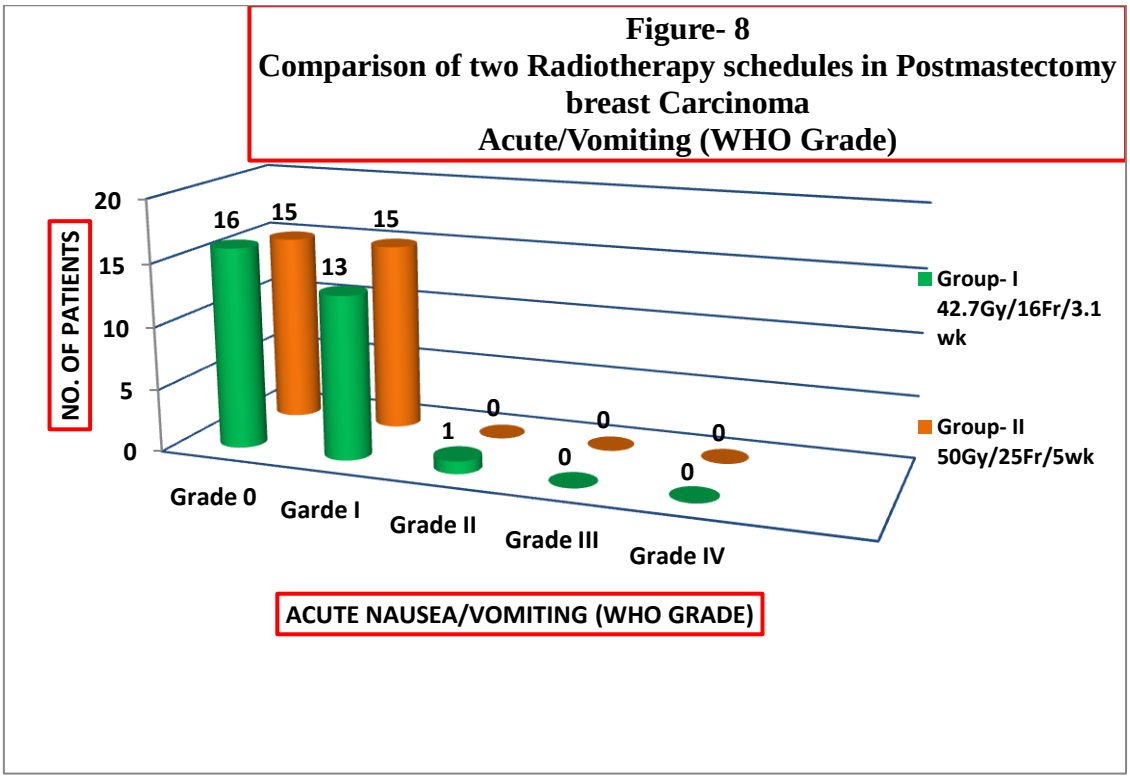
1. Acute Radiation Reactions – Skin reactions

Acute skin reactions noted in all 60 patients at 15th day and 1 month after completion of treatment. The same are given here in figure-7. The highest grade noted in Group I was grade II in 30% patients and grade IV in 1 patient of group II. The difference in the fortnightly assessment of skin reactions was not statistically significant.



2. Acute Radiation Reactions – Nausea and Vomiting

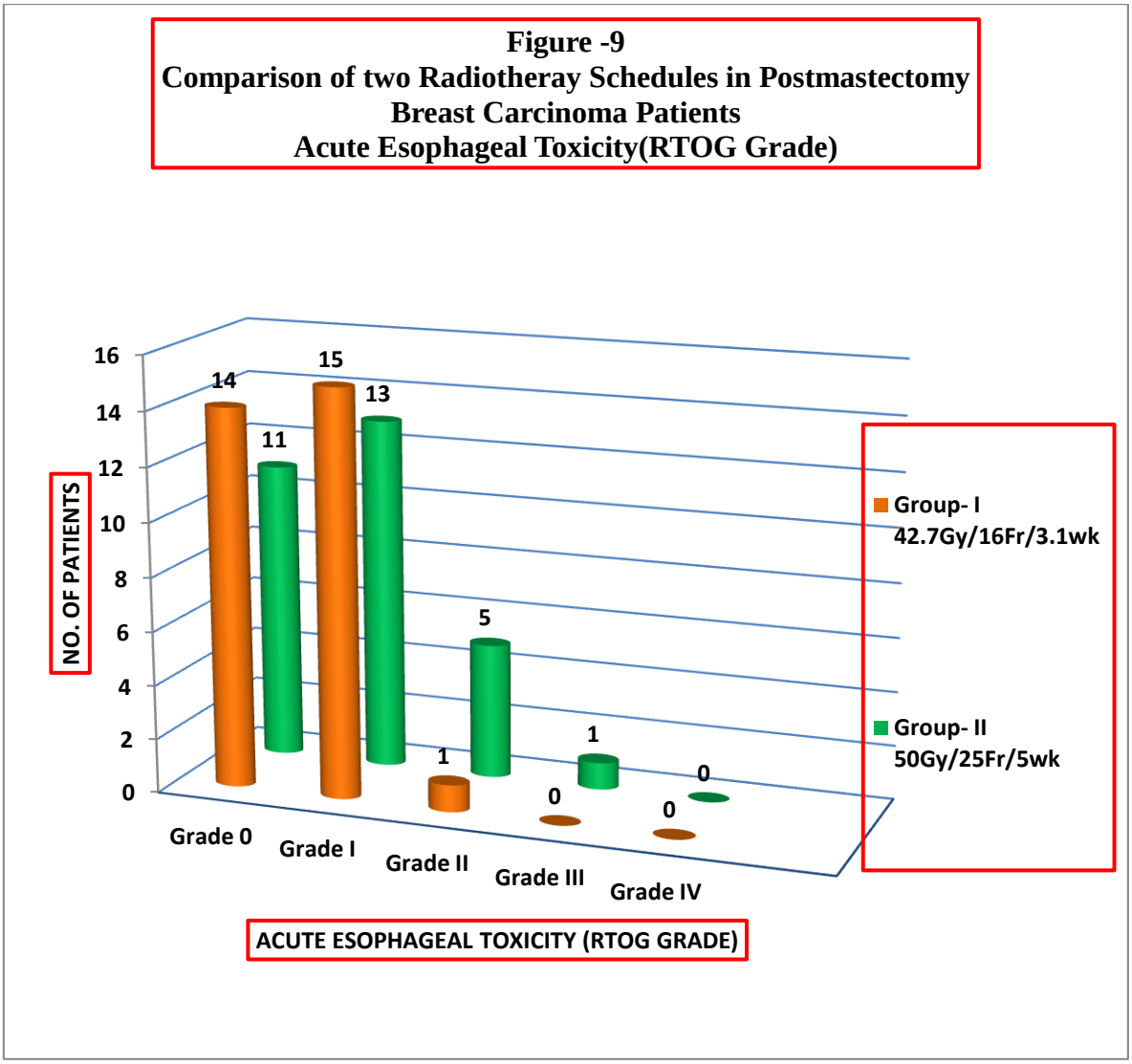
Nausea and vomiting was graded as per WHO criteria and noted on 15th day and 1 month after treatment. The same is given in Table-10, figure 8, the highest grade noted overall was Grade II seen in 1 patient of group I. The most common reaction was Grade I nausea and vomiting seen in 43.3% and 50% of group I and group II patients. The fortnightly assessment of nausea and vomiting was not significant statistically.



3. Acute Radiation Reactions - Esophageal Toxicity

Esophageal reactions noted on day 15th and 1 month after completion of treatment and summarized here in figure-9. The highest grade noted overall was grade I in 46.7% patients, with statistically no significant difference in the two groups.

Figure -9
Comparison of two Radiotheray Schedules in Postmastectomy Breast Carcinoma Patients
Acute Esophageal Toxicity(RTOG Grade)



4. Late Radiation Reactions (RTOG Criteria): Skin and Subcutaneous Reactions

Late radiation toxicity was observed in both the groups and summarized Figures-10A and 10B. Highest grade of occurrence during the course of six months follow-up for late radiation reactions was noted. Skin toxicity was the most common late toxicity noted with Grade I being the highest grade of occurrence in 19 (63.3%) and 13 (43.3%) patients of Group I and Group II respectively. Grade II late skin toxicity was the highest grade of occurrence in 4 (13.4%) patients in Group I and 5 (16.7%) patients in Group II. The second most common late toxicity was subcutaneous toxicity with highest grade of occurrence being Grade I, reported in 17 (56.7%) and 12 (40%) patients in Group I and Group II respectively followed by grade II subcutaneous toxicity which was observed in 5 (16.6%) patients of both the groups.

Figure -10A
Comparison of Two Radiotherapy schedules in Postmastectomy Breast Carcinoma Patients
Late Skin Toxicity(RTOG Grade)

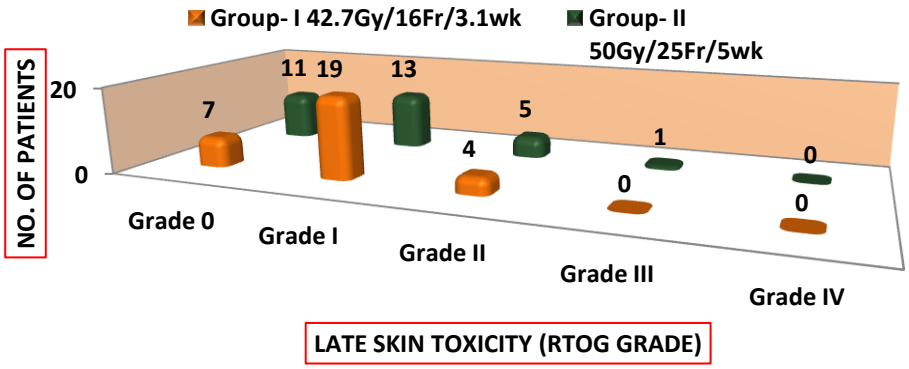
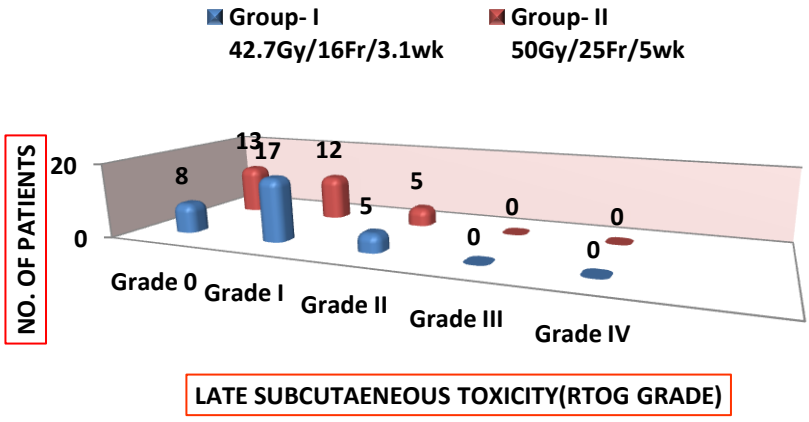


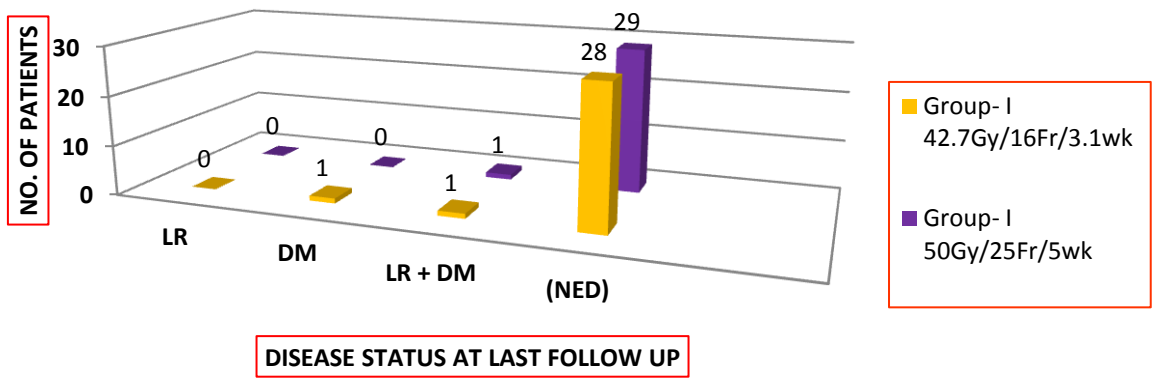
Figure - 10B
Comparison of two Radiatherapy Schedules in Postmastectomy Breast carcinoma patients
Late Subcutaeneous Toxicity (RTOG Grade)



Disease Status at Last Follow Up

The details of disease status at the completion of treatment and last follow up (with median follow up of 10 months) are shown in Figure-11. Fifty seven out of 60 (95%) patients had no evidence of disease at last follow up. Patients were followed up for 6 to 14 months with a median follow-up of 10 months. No evidence of disease at last follow up in Group I and Group II was 93.3% and 96.7% respectively. Both local recurrence and distant metastases was seen in 1(3.3%) patient at 7th month of follow-up in group I and 1(3.3%) patient at 8th month of follow-up. 1(3.3%) patient in Group I developed only distant metastases at 10th month follow-up. Intergroup in disease status at last follow up was statistically not significant among both the groups.

Figure -11
Comparison of Two Radiotherapy schedules in Post Mastectomy Breast Carcinoma Patients
Disease Status at Last Follow Up (n=60)



Compliance

All 60 patients were compliant with their intended treatment with radiotherapy.

Discussion

Carcinoma breast has been found to be the leading cancer affecting women in the world in 2018 (11.6%)[1] & also among women in Haryana (9.1% in 2018 in the Department of Radiotherapy, PGIMS, Rohtak)[2]. Due to the advanced stage at presentation or less availability of clear margins at surgery, the most commonly performed surgery still, is the modified radical mastectomy. Post operative radiation therapy to chest wall forms an integral part of treatment to prevent locoregional relapse. Conventional fraction radiotherapy has been limited by low patient compliance, unplanned interruptions due to long treatment duration or long travelling distances and high cost of treatment. The reports of several randomised trials to date have revealed that a modest increase in dose per fraction plus minimal decrease in total dose could have comparable effects on safety and efficacy as that of conventional fractionation.[3] Thus this study was planned to evaluate the comparative efficacy of hypofractionation (42.7Gy) and conventional radiation (50Gy) therapy especially in carcinoma breast patients who have specifically undergone modified radical mastectomy.

Acute Radiation Toxicity

Radiation therapy sequel after post mastectomy radiation therapy are a function of irradiated volume, total dose and fractionation. Various side effects of radiation treatment include acute and late reactions. Acute radiation reactions, we assessed in our study were skin toxicity, nausea/vomiting and esophageal reactions.

Lopez et al studied in patients treated with postoperative radiation therapy after mastectomy using a standardized ^{60}Co technique. The dose delivered was 50 Gy over a period of 5 weeks, in daily fractions of 2 Gy. The most frequent acute complications found were erythema (91.7%), dry desquamation (29.6%) and moist desquamation (35.2%).[4] These results match with our study as in both the groups, grade I skin reaction was the most common toxicity reported.

The studies by Bentzen et al, the START A and START B trials found that the acute skin reactions were less common in the hypofractionated arm than in the conventional radiation therapy arm. They also reported that normal tissue effects did not differ significantly between the two arms. [5-6]

UK FAST Trial results show evaluable patients with grade 3 RTOG toxicity were: 40Gy/15F 6/44 (13.6%); 27Gy/5F 5/51 (9.8%); 26Gy/5F 3/52 (5.8%). In the second sub study, evaluable patients with grade 3 CTCAE toxicity were:

40Gy/15F 0/43; 27Gy/5F 1/41 (2.4%); 26Gy/5F 0/53, corroborating with the results of this study.[7]

Nausea and vomiting were observed weekly during the treatment and also at the completion of treatment and graded as per RTOG criteria. Most common toxicity reported was grade I, seen in 10 (33.3%) patients in both the groups. Grade II toxicity was reported in 3 (10%) patients group I and none in group II. No patient in both the groups reported grade III and IV nausea and vomiting. The difference in weekly assessment of nausea and vomiting was statistically not significant between the two groups.

Acute esophageal reactions were observed weekly during the treatment and also at the completion of treatment. Most common toxicity reported was grade I seen in 53.3% and 43.3% in Group I and Group II respectively. Grade II toxicity was reported in 3 patients in Group I and 1 patient in Group II. 2 patients in Group I and 1 patient in Group II reported grade III esophageal reactions while no patient in either group had Grade IV reactions. The difference in weekly assessment of esophageal reactions was statistically not significant between the two groups.

The study by Kumbhaj et al, reported that difficulty in swallowing and nausea/vomiting were the most common acute toxicity reported after skin toxicity. The incidence of these toxicities did not differ significantly between the conventional and hypofractionated arms.[8] The observations in the present study match with the results of this study.

Late Radiation Toxicity

Late radiation toxicity observed in both the groups. Subcutaneous toxicity was the most common late toxicity, grade I was observed in 36.7% and 23.3% in Group I and Group II respectively. Grade II late subcutaneous toxicity was observed in 13.3% patients in Group I and 6.7% patients in Group II. Grade I skin reaction was reported by 7 (23.3%) patients in Group I and 3 (10%) patients in Group II. Grade II skin reactions were seen in 2 patients in both the groups.

The study by Elsayed et al stated that hypofractionated radiation was safe and showed acceptable toxicity rate.[9] Incidence of late skin toxicity and radiation induced pneumonitis were comparable between hypofractionated and conventional radiation arms. Eldeeb et al compared three fractionation schedules in post mastectomy patients enrolled into three groups. Although acute skin reactions were higher in the hypofractionated arms, there was no significant difference in the local recurrence rates or late radiation effects.[10]

Disease Status at Last Follow up

Fifty seven out of 60 (95%) patients had no evidence of disease (NED) at last follow up. No evidence of disease at last follow up in Group I and Group II was 93.3% and 96.7% respectively. Both local recurrence and distant metastases together was seen in 1(3.3%) patient each in both the groups and 1(3.3%) patient in Group I developed distant metastases alone. The difference in disease status at last follow up was statistically not significant among both the groups. An update of the Canadian trial showed that, results have not changed after a 10- year follow up, when the probability of overall survival was similar in hypofractionated and conventional fractionation group (p=0.79). The START A trial and START B trial also reported that, there was no evidence that any hypofractionated radiotherapy regimen was associated with a worse overall survival rate. In this study the 4-years disease free survival (DFS) rate for both groups was 87% (81% and 92% for conventional fractionation and hypofractionation, respectively p=0.47).[11] At last follow up (with a median follow up of 10 months), 6.7% patients had local recurrence only, in Group I (Stages IIIA and IIIB) and Group II (Stage IIB and IIIB). One patient (3.3%) in Group I had Distant metastases alone (stage IIB) and 1 patient each (3.3 %) in both the groups (Stage IIA and IIIA) had both local recurrence and distant metastases.

The Early Breast Cancer Trialists Collaborative Group (EBCTCG), meta-analysis of 78

prospective randomized clinical trials investigated mastectomy with and without post operative radiotherapy, the addition of post mastectomy radiation therapy provided similar proportional reductions in local recurrence regardless of patient age, tumor characteristics, use of systemic therapy, although the absolute risk reduction was larger in the higher-risk populations. The 5-year local recurrence risks in lymph node negative patients with and without post mastectomy radiation therapy were 2% and 6%, respectively, with a 3.6% decrement in 15-year breast cancer mortality.[12]

Rastogi et al also reported that at a median follow-up of 20 months, almost similar results were seen in both the groups in terms of toxicity, tolerability, and locoregional control. Adjuvant postmastectomy HF RT was found to be well tolerated with mild-to-moderate side effects that neither reached statistical significance nor warranted any treatment interruption/ hospitalization.[13]

Conclusion

Statistics regarding local control achieved, recurrent/metastatic disease, types and frequency of radiation reactions encountered have been reported. All the patients completed intended radiation treatment. In terms of local control and side effects almost similar results were seen in both the groups. However, acute and late reactions in the hypofractionation group (Group I) were higher than in the conventional fractionation group (Group II). Conventional fractionation schedule has got the disadvantage of extending the treatment for 5 weeks, which is inconvenient to the patient and utilizes most of the limited radiation resources in a busy radiotherapy centre, resulting in long waiting lists. Whereas hypofractionated schedules have shown same response in terms of tumor control and late normal tissue effects resulting in decreased workload, increased compliance and reduced cost of treatment, so it can be considered as a reliable alternative in radiation treatment for post mastectomy carcinoma breast patients. However the follow up of these patients is continuing in the Department of Radiotherapy, PGIMS Rohtak for further analysis at a later period of time to throw some definite light on patterns of failure, overall survival and long term toxicity of hypofractionated radiation therapy.

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