Original Article

A Comparative Study of Hypofractionated and Conventional Radiotherapy in Postmastectomy Breast Cancer Patients

Kartick Rastogi, Sandeep Jain, Aseem Rai Bhatnagar, Sandeep Bhaskar, Shivani Gupta, Neeraj Sharma

Department of Radiotherapy, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India

Corresponding author: Dr. Kartick Rastogi, MD, Radiotherapy

Department of Radiotherapy, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India

Tel: +917014774941; Fax: 911412569885

E-mail: kartickkashyap@gmail.com

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ABSTRACT

Objective: The aim of this study was to compare toxicity and locoregional control of short duration hypofractionated (HF) radiotherapy (RT) with conventional RT in breast cancer patients. **Methods:** A total of 100 postmastectomy breast cancer patients were randomized for adjuvant RT in control group (comprising fifty patients who received the standard conventional dose of 50 Gy in 25 fractions with 2 Gy per fraction) and study group (comprising fifty patients who received HF RT with dose of 42.72 Gy in 16 fractions with 2.67 Gy per fraction). All patients were treated on linear accelerator with 3-dimensional conformal RT technique. Outcome was analyzed in terms of toxicity, tolerability, and locoregional control. **Results:** In the present study, 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. **Conclusions:** HF postmastectomy RT is comparable to conventional RT without evidence of higher adverse effects or inferior locoregional tumor control and has an added advantage of increased compliance because of short duration; hence, it can help in accommodating more breast cancer patients in a calendar year, ultimately resulting in decreased waiting list, increased turnover, and reduced cost of treatment.

Key words: Conventional fractionated radiotherapy, hypofractionated radiotherapy, postmastectomy radiotherapy, three-dimensional conformal radiation therapy

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Introduction

Breast cancer is the most common cancer in females.[1] In India, especially Rajasthan, most of the patients present with locally advanced breast cancer unlike the western world, so mastectomy is performed more often than breast conservative surgery (BCS). Most of these patients require postmastectomy radiotherapy (PMRT) to decrease locoregional recurrence.[2-5] PMRT is recommended in patients with 4 or more positive axillary lymph nodes (ALN) and should be strongly considered in patients with 1–3 positive ALN. In patients with negative nodes, PMRT is indicated for tumors more than 5 cm or positive/close pathological margins.[6] The normally used conventional fractionated chest wall radiotherapy (CF RT) uses 2 Gy daily fractions for 5–6 weeks. Many a times, patients discontinue treatment in between due to financial constraints or some other reasons which ultimately affects the treatment outcome. Such a long treatment schedule has major implications on both patient's compliance and department workload, especially in a country like India where money, workforce, and resources are always a constraint. There has been a growing trend toward HF which involves delivering a higher dose per fraction for a shorter number of fractions for a biologically equivalent dose while maintaining the same toxicity and locoregional control rates. While many randomized trials have confirmed the noninferiority results of hypofractionated RT (HF RT) in post-BCS patients,[7-10] its role has not yet been established for postmastectomy breast cancer patients. Moreover, as far as Indian patients are concerned, the data on HF PMRT are limited. This short HF RT schedule using 2.67 Gy daily fractions for 3–3.5 weeks would be most convenient for patients, especially those coming from remote areas to the RT facilities in addition to health-care providers, as it would increase the turnover in the department without compromising the treatment outcome.[11-16] In this context, the present prospective study was carried out in the Department of RT, SMS Medical College, Jaipur, from December 2014 to May 2016, with an aim to compare the toxicity, tolerability, and locoregional control in postmastectomy breast cancer patients with conventional versus HF RT. A total of hundred patients were randomly distributed among CF and HF group. In the current study, we used HF dose of 42.72 Gy with 2.67 Gy per fraction, which is matched with the recommended biologically equivalent dose of 50 Gy in 2 Gy per fraction.

Methods

Patient selection

The present prospective study was carried out in the Department of RT, SMS Medical College and Attached Group of Hospitals, Jaipur, Rajasthan, India to compare HF RT with conventional RT. One hundred previously untreated postmastectomy patients older than 18 years with histologically confirmed infiltrating duct carcinoma of unilateral breast without evidence of distant metastasis or second malignancy, with normal functioning cardiac, renal, and pulmonary functions with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2 were randomized into CF and HF group with fifty patients falling in each group.

Evaluation of patients

All patients underwent complete physical examination and routine blood counts, biochemistry, contrast-enhanced computed tomography of chest and whole abdomen before starting the treatment. Bone scan was done as per indications. All patients were reviewed on a weekly basis while the RT was going on, and on monthly basis after the completion of RT for a period of 6 months, and thereafter for every 3 months till the last follow-up. During each clinical visit, patients were assessed for development and severity of any acute or chronic toxicity including skin toxicity, pulmonary toxicity, dysphagia, and lymphedema. All toxicities were graded according to RTOG Acute and Late Radiation Morbidity Scoring Criteria and the worst grade was reported.

Radiotherapy protocol

All patients were randomly distributed into two treatment groups: CF group = 50 patients (50 Gy/25 fractions, 2 Gy per fraction, one fraction per day, 5 fractions per week, for 5–6 weeks) and HF group = 50 patients (42.72 Gy/16 fractions, 2.67 Gy per fraction, 1 fraction per day, 5 fractions per week, for 3–3.5 weeks).

Dosimetric analysis

All patients were planned on Siemens Oncor Expression linear accelerator machine with three-dimensional conformal radiation therapy technique. Some patients were treated with single-beam energy, whereas in others, a combination of both 6 and 15 MV beam was used depending on patients' anatomy. The treatment was planned with a goal of 100% volume of Planning Target Volume (PTV) to be covered by 95% isodose line. Data collected included the volume of PTV receiving at least 95% and 90% of prescribed dose (V95 and V90) and also dose delivered to 90% of the volume of PTV (D90%) from the dose-volume histograms. The acceptable hot spot limit was 107%. The treatment plan was accepted if the volume of heart receiving 25Gy was ≤10% (i.e. V25 heart ≤10%) and the volume of ipsilateral lung receiving 20 Gy was ≤35% (i.e. V20 ipsilateral lung ≤35%).

Statistical analysis

For statistical analysis, all data were recorded and analyzed on Microsoft Excel 2007 and Statistical Package for Social Sciences (SPSS) trial version 20.0 (IBM Corp., Armonk, New York, USA). Chi-square was used for all categorical data. *P* value reports were two tailed and an alpha level of 0.05 was used to assess statistical significance. Sample size selection was limited due to time and resource constraints, so all postmastectomy breast cancer patients who consented for the study in the given time frame were selected and randomized into CF group and HF group. Method of randomization was chit in box method with replacement.

Results

Only postmastectomy patients were included in the study. The two groups were almost even in the distribution of their tumor and clinical characteristics. In both the groups, most of the patients were younger than 50 years with ECOG PS 1 belonging to urban background [Table 1]. In CF group, stage IIB tumors of left breast whereas in HF group, stage IIA tumors of right breast were more common. In both groups, most of the tumor were poorly differentiated (Grade III) infiltrating ductal carcinoma located in upper outer quadrant, and were estrogen receptor positive, progesterone receptor negative, and human epidermal growth factor receptor 2 negative. The median number of lymph nodes dissected was 14 in CF group and 15 in HF group, whereas the median number of positive lymph nodes was 2 in both groups [Table 2].

All patients tolerated RT well. All patients completed postmastectomy radiation therapy. Treatment interruption was not significantly different among the two groups and was seen in 6 patients in CF group (median 4 days, range 2–5 days) and 10 patients in HF group (median 6 days, range 3–8 days).

Supraclavicular fossa was irradiated in 42 (84%) patients in CF group and 43 (86%) patients in HF group. Neoadjuvant chemotherapy (NACT), adjuvant chemotherapy (CT), and hormonal therapy were given to 58%, 96%, and 58% patients in CF and 52%, 98%, and 54% patients in HF group, respectively. The mean heart dose among patients with left- and right-sided breast cancer was 4.86 Gy versus 0.57 Gy in CF group and 6.25 Gy versus 1.12 Gy in HF group, respectively. V25 for left and right heart was 8.77% and 0% in CF and 9.12% and 0% in HF group, respectively. V20 for ipsilateral lung was 20.85% in CF and 24.25% in HF group and the mean lung dose was 10.57 Gy for CF and 10.64 for HF group [Table 3].

Treatment toxicities were found to be comparable between the two groups [Table 4]. Grade I was the most common grade for acute and chronic dermatitis, dysphagia, and pneumonitis, whereas for lymphedema, most common reactions were Grade II. No patient in either group developed Grade III and IV late radiation side effects.

Follow-up period ranged from 11 months to 27 months with a median follow-up of 20 months. Disease status in the form of local (chest wall) recurrence, regional (nodal) recurrence, distant metastasis, and no evidence of disease was documented as per the last follow-up [Table 5]. The locoregional outcome and survival were found to be comparable in both the groups. The site of nodal recurrence was supraclavicular lymph node and that of distant metastasis was brain (3%), bone (1%), lung (1%), and liver (1%). None of the patient developed second malignancy including cancer of the opposite breast. No death was reported in either group till last follow-up [Table 6].

Table 1: Patient characteristics

Patient characteristics	Control group, *n* (%)	Study group, *n* (%)	χ^2	*P*	Significance
Age (year)					
Median	46	50	1.22	0.88	Not significant
Range	21-66	21-79			
SD	11.45	11.72			
Residence					
Rural	22 (44)	19 (38)	0.37	0.54	Not significant
Urban	28 (56)	31 (62)			
ECOG PS					
0	3 (6)	1 (2)	1.19	0.55	Not significant
1	40 (80)	43 (86)			
2	7 (14)	6 (12)			
Menopausal status					
Pre	16 (32)	13 (26)	0.44	0.51	Not significant
Post	34 (68)	37 (74)			

ECOG: Eastern Cooperative Oncology Group, PS: Performance status, SD: Standard deviation

Discussion

SMS Hospital is the largest hospital of our state and patients from all over the state as well as from nearby states come to our department. Breast cancer is the second most common cancer among female cancer patients presenting in our department. Due to longer treatment time in CF, many patients cannot get RT timely due to overburdened department. For 25 fractions protocol, 75 fields have to be treated. In contrast, for 16 fractions, the number of fields is reduced to 48 only. This saves about 80–90 min if average time for setting one field is taken as 3 min. Therefore, if 20 patients of breast cancer are being treated in 1 day, approximately 20–30 working hours can be saved. This would result in substantial economic benefit. Some patients have no places to live while the therapy is going on and have to be admitted in the wards. With the HF RT, the patient has

Table 2: Tumor characteristics

Tumor characteristics	Control group, *n* (%)	Study group, *n* (%)	χ^2	*P*	Significance
Anatomical side					
Left	26 (52)	21 (42)	1.00	0.32	Not significant
Right	24 (48)	29 (58)			
Quadrant of breast involved					
UOQ	22 (44)	21 (42)	0.2	0.99	Not significant
UIQ	6 (12)	7 (14)			
Central	13 (26)	14 (28)			
LOQ	5 (10)	5 (10)			
LIQ	4 (8)	3 (6)			
Grade					
I	4 (8)	1 (2)	2.67	0.26	Not significant
II	21 (42)	18 (36)			
III	25 (50)	31 (62)			
AJCC stage					
IIA	15 (30)	14 (28)	4.08	0.39	Not significant
IIB	18 (36)	13 (26)			
IIIA	11 (22)	13 (26)			
IIIB	0	3 (6)			
IIIC	6 (12)	7 (14)			
T stage					
T1	2 (4)	4 (8)	2.78	0.43	Not significant
T2	42 (84)	35 (70)			
T3	5 (10)	9 (18)			
T4	1 (2)	2 (4)			
N stage					
N0	15 (30)	13 (26)	1.60	0.66	Not significant
N1	20 (40)	16 (32)			
N2	9 (18)	13 (26)			
N3	6 (12)	8 (16)			
ER					
Positive	29 (58)	27 (54)	0.16	0.69	Not significant
Negative	21 (42)	23 (46)			
PR					
Positive	21 (42)	20 (40)	0.04	0.84	Not significant
Negative	29 (58)	30 (60)			
HER 2/neu					
Positive	7 (14)	8 (16)	0.49	0.78	Not significant
Negative	29 (58)	31 (62)			
Unknown	14 (28)	11 (22)			

UOQ: Upper outer quadrant, UIQ: Upper inner quadrant, LIQ: Lower inner quadrant, LOQ: Lower inner quadrant, ER: Estrogen receptor, PR: Progesterone receptor, HER 2: Human epidermal growth factor receptor 2, AJCC: American Joint Committee on Cancer, T: Primary tumor, N: Regional lymph nodes

Table 3: Treatment protocol

	CF group, *n* (%)	HF group, *n* (%)
Number of patients	50	50
Radiation dose (Gy)	50	42.72
Number of fractions	25	16
Dose per fraction (Gy)	2	2.67
SCF irradiation	42 (84)	43 (86)
NACT	29 (58)	26 (52)
Adjuvant CT	48 (96)	49 (98)
Hormonal therapy	29 (58)	27 (54)
V25 left heart (%)	8.77	9.12
V20 I/L lung (%)	20.85	24.25

SCF: Supraclavicular fossa, NACT: Neoadjuvant chemotherapy, CT: Chemotherapy, CF: Conventional fractionated, HF: Hypofractionated

to stay for 20 days in contrast to 35 days, so this protocol is very advantageous both for the patients and the institute.

On the other hand, HF with larger radiation dose per fraction increases the possibility of late normal tissue damage. However, the linear-quadratic model predicts that the normal tissue toxicity is not increased when the fraction dose is modestly increased and the total dose is reduced, as in our case. This is confirmed by results of many trials where HF RT protocols are as effective as the CF RT, regardless of disease stage or type of breast surgery. Finally, the HF RT schedule would be more convenient for patients (especially those coming from remote areas to RT departments) and for

Table 4: Treatment toxicities

Treatment characteristics	Control group, *n* (%)	Study group, *n* (%)	χ^2	*P*	Significance
Acute dermatitis					
Nil	4 (8)	1 (2)	1.90	0.39	Not significant
Less than Grade II	26 (52)	28 (56)			
Greater than or equal to Grade II	20 (40)	21 (42)			
Chronic dermatitis					
Nil	41 (82)	43 (86)	0.38	0.83	Not significant
Less than Grade II	7 (14)	5 (10)			
Greater than or equal to Grade II	2 (4)	2 (4)			
Dysphagia					
Nil	37 (88)	36 (84)	0.40	0.82	Not significant
Less than Grade II	4 (10)	6 (14)			
Greater than or equal to Grade II	1 (2)	1 (2)			
Radiation pneumonitis					
Nil	40 (80)	44 (88)	1.52	0.47	Not significant
Less than Grade II	7 (14)	5 (10)			
Greater than or equal to Grade II	3 (6)	1 (2)			
Lymphedema					
Nil	44 (88)	43 (86)	0.10	0.95	Not significant
Less than Grade II	1 (2)	1 (2)			
Greater than or equal to Grade II	5 (10)	6 (12)			

Table 5: Disease status at last follow-up

Status at last follow-up	Control group, *n* (%)	Study group, *n* (%)	Overall, *n* (%)	χ^2	*P*	Significance
No evidence of disease	47 (94)	45 (90)	92 (92)	0.54	0.46	Not significant
Local (chest wall) recurrence	1 (2)	0	1 (1)	1.01	0.31	Not significant
Regional (nodal) recurrence	0	1 (2)	1 (1)	1.01	0.31	Not significant
Distant metastasis	2 (4)	4 (8)	6 (6)	0.71	0.40	Not significant
Death	0	0	0	-	-	-

health-care providers, as it would increase the turnover in RT departments. In our study, patients treated with HF RT were safe and showed acceptable and manageable toxicity rate and locoregional control.

Grade I was the most common grade of acute radiation dermatitis in both the groups, with an incidence of 52% in CF group and 56% in HF group. Grade II or higher acute dermatitis had an incidence of 40% in CF group and 42% in HF group. This was higher than what has been reported by Pinnaro as he reported 4 out of 39 (10.2%) patients had GII dermatitis. However, this was much less than that reported by Taher *et al.*,[17] as they reported 86.7% in 42.4 Gy arm with 40% GII or more because they studied on BCS patients only. This was in agreement with the study of Ali *et al.*,[13] who reported 24% incidence of Grade II dermatitis and resulted in only 1 week treatment interruption compared with 9% in CF with 10 days interrupted treatment. Grade II chronic radiation dermatitis was 4% in both groups which is matched with Whelan *et al.*[18] as they reported 2.6% Grade II skin complication; however, this was in total disagreement with Yarnold *et al.*[19] who reported 83% because they studied on BCS patients only.

Grade II or higher radiation-induced pneumonitis was found in 6% of CF group and 2% of HF group. These findings are in agreement with Pinitpatcharalert *et al.*,[20] Shaltout and El Razek,[21] Plataniotis[22] evaluated radiation pneumunitis in HF setting (42.5 Gy/16 Fr) by HRCT in early breast cancer patients and reported minimal and minor effects on the underlying lung parenchyma. Shahid *et al.* has reported a 5% and Shaaban[23] 4.7% incidence of radiation pneumonitis with 40 Gy/15 fraction protocol. Lingos *et al.*[24] and Ibrahim *et al.* have reported incidences of radiation pneumonitis to be 2.9% and 2.7%, respectively. In contrast, Lind *et al.*[25] and Hanna *et al.*[26] reported that 9%–15% of patients had radiation pneumonitis. The difference could be explained on the ground that Lind *et al.* irradiated internal mammary nodes in 95% of patients, and 21% of patients received CMF regimen which contains methotrexate with high tendency to cause pulmonary complications. In addition, Hanna *et al.*[26] used adjuvant paclitaxel-containing CT, which is known to reduce the lung tolerance.

Lymphedema is an established complication of both ALN dissection (ALND) and axillary RT. Almost two-third

Table 6: Association of recurrence with various parameters

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Group	CF	CF	CF	HF	HF	HF	HF	HF
Radiation dose (Gy)	50	50	50	42.72	42.72	42.72	42.72	42.72
Dose per fraction (Gy)	2	2	2	2.67	2.67	2.67	2.67	2.67
Type of recurrence	Local	DM	DM	Regional	DM	DM	DM	DM
Site of recurrence	Chest wall	Lung, bone	Liver, bone	SCF	Brain	Brain, lung	Brain, liver	Brain
Age (year)	35	62	43	60	45	39	36	65
ECOG PS	1	1	1	1	2	1	1	2
Residence	Rural	Urban	Rural	Urban	Rural	Urban	Urban	Rural
Menopausal	Pre	Post	Pre	Post	Pre	Pre	Pre	Post
Side	Right	Left	Right	Right	Right	Right	Left	Left
Quadrant	C	C	UOQ	UOQ	UIQ	C	UOQ	UIQ
Grade	III	III	II	III	III	III	III	III
T	T2	T2	T2	T3	T2	T3	T2	T2
N	N2	N1	N1	N3	N2	N0	N3	N2
Stage	IIIA	IIB	IIB	IIIC	IIIA	IIB	IIIC	IIIA
LN dissected	24	18	17	14	14	29	15	16
LN+	4	1	4	14	5	0	12	6
ER	+	+	+	+	-	-	+	-
PR	+	+	+	+	-	-	-	-
HER 2/neu	?	-	-	+	-	-	?	-
Time for relapse (month)	11	9	16	13	7	7	5	14

LN: Lymph nodes, ER: Estrogen receptor, PR: Progesterone receptor, HER 2: Human epidermal growth factor receptor 2, CF: Conventional fractionated, HF: Hypofractionated, UOQ: Upper outer quadrant, UIQ: Upper inner quadrant, C: Central quadrant, DM: Distant Metastasis, SCF: Supraclavicular fossa, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, +: Positive, -: Negative, ?: Unknown

patients never developed this problem in any of the protocols whereas Grade II or higher lymphedema was seen in 10% patients in CF group and 12% in HF group. At Memorial Sloan Kettering Cancer Center, the experience from 1977 to 1979, based on a cohort of 20 years breast cancer survivors, measurable lymphedema was documented to be 31%. Meek[27] reported 2%–5% of lymphedema when radiation alone was given to the axilla. Chua *et al.*[28] reported 9.5% arm edema with axillary dissection, 6.1% with radiation, and 31% when the two modalities were combined ($P < 0.001$). In a comprehensive review, Erickson *et al.*[29] reported 26% lymphedema after breast cancer treatment. Petrek and Heelan[30] in seven selected reports showed lymphedema in the range of 6%–30%.

Conclusion

We conclude that HF PMRT is comparable to conventional RT without evidence of higher adverse effects or inferior locoregional tumor control; hence, it can be offered as a safe and effective alternative to conventional RT for postmastectomy breast cancer patients in adjuvant settings. When the treatment is completed in shorter time period, interruption unrelated to treatment is reduced ultimately increasing the efficacy of the treatment. HF, with short duration of treatment, has an added advantage of increased compliance; hence, it can help in accommodating more breast cancer patients in a calendar year, ultimately resulting in decreased waiting list, increased turnover, and reduced cost of treatment. It is of utmost importance in a resource limited country like ours that is already flooded with cancer patients.

The major limitations of the present study are small number of patients and comparatively short period of follow-up. We recommend similar studies with large number of patients and longer follow-up period in the future.

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Conflicts of interest

There are no conflicts of interest.

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