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Original Article

Hypofractionated radiotherapy in breast cancer: Is it safe?

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ABSTRACT

Introduction: Radiation therapy has gained an established role in the treatment of breast cancer either as chest wall irradiation after modified radical mastectomy, or as whole breast irradiation after a breast conserving surgery (BCS). For patients with resectable tumour undergoing mastectomy, radiation therapy to chest wall and regional lymph nodes to a total dose of 5000-6000 cGy is usually employed. The aim of the present study was to assess a hypofractionated RT regimen of 42.5Gy/16#/3wks versus the conventional RT regimen of 50Gy/25#/5wks in post mastectomy patients of breast cancer in our institute and to compare the acute and late toxicities as well as effectiveness with conventional method. **Materials and methods:** Thirty women of breast cancer, who were post mastectomy were assigned to receive 42.5 Gy/ 16#/3wks and for comparison, a group of 30 patients with similar characteristics were treated with conventional fractionation and received 50 Gy/25#/5 wks. **Results:** The grade 2 and 3 skin toxicity in group A was 13.33% and 10% respectively. Grade 4 toxicity was not seen. group B had grade 2 in 6.7% patients. No patient had grade 3 and 4 toxicity in group B. Grade 1 lymphoedema was seen in 53%, grade 2 in 30% and grade 3 in 6.7% patients in group A and 53%, 20% and 16.7% in group B respectively. On HRCT, chest for lung toxicity, group A had ground glass appearance in 3.4% patients, pleural thickness in 10.4% and septal lines, linear opacifications and subpleural opacities were seen in 58.6% patients. In group B, it was 6.7%, 13.3% and 36.7% respectively. **Conclusion:** The hypofractionated protocol can be safely used as the toxicities and effectiveness are comparable to the conventional radiotherapy in post mastectomy breast cancer patients. Hypofractionated radiotherapy was cost effective and more convenient to the patients as the use of 16 fractions (instead of 25), saves 900 treatment sessions per 100 patients (2500-1600=900). This corresponds to an additional number of 56 (900:16) patients that could be treated by the same number of fractions.

Key words: Breast cancer; High resolution computed tomography; Hypofractionation; Radiotherapy

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INTRODUCTION

Radiation therapy has gained an established role in the treatment of breast cancer in the form of chest wall irradiation for high risk patients after modified radical mastectomy, or as whole breast irradiation for patients after a breast conserving surgery. This therapy reduces the risk of local relapse and breast cancer mortality. Moreover it has also formally been confirmed that the improved local control translates into a better cancer specific and overall survival, validating the crucial role of radiotherapy in the primary treatment of non-metastatic breast cancer.^{1,2} The challenge now is to minimise the morbidity caused by treatment without losing its efficacy.^{3,4} Sensitivity to fraction size is conveniently described by the α/β value, which is relatively high (>6Gy) for many squamous carcinomas and early responding normal tissues compared to late responding normal tissue (α/β value<6Gy). This relationship does not apply to all tumour types, with evidence that adenocarcinomas of the breast

and prostate are more sensitive to fraction size than previously thought. Recent studies have demonstrated that the α/β ratio for breast carcinoma is close to 4 and the α/β ratio for normal breast tissue is approximately 3.4.^{5,6-8} Therefore there is both theoretical and clinical evidence to support the hypothesis that a modest increase in the dose per fraction coupled with a modest decrease in the total dose may be a safe and effective way to improve local care as compared to the traditional 2 Gy per fraction schedule.⁹⁻¹¹ This approach is based on the radiobiological linear quadratic model, according to which a larger dose per fraction schedule given over a shorter period is just as effective as the conventional schedule.¹² Moreover the hypofractionated schedule has significant implications for patient convenience and resource utilization. For patients with resectable tumour undergoing mastectomy, radiation therapy to chest wall and regional lymph nodes to a total dose of 5000-6000 cGy is usually employed.¹³ In view of this, the present study was planned and commenced to compare a

hypofractionated RT regimen of 42.5Gy/16#/3wks versus the conventional RT regimen of 50Gy/25#/5wks in post mastectomy patients of breast cancer in our institute in terms of skin, haematological and pulmonary toxicities.

MATERIAL AND METHODS

The present randomised prospective study was conducted among 60 patients histologically proven of breast cancer in Department of Radiotherapy, Guru Gobind Singh Medical College and Hospital, Faridkot from April 2015 to May 2016. The study compared conventional RT regimen, which is already being followed at our centre, versus a hypofractionated regimen in post mastectomy patients of carcinoma breast. Ethical approval was obtained from the institutional ethical committee. All patients were subjected to detailed history after taking written and informed consent and complete physical examination was done. Eligibility criteria consisted of biopsy proven, stage IIA to IIIC, postmastectomy and patients with age less than 70 years. Patients with breast lymphoma, stage IV disease ,prior radiotherapy, pregnant and lactating females were excluded from the study The patients were randomised in two groups. Randomisation was done by central randomisation technique. The first group (A) received Conventional RT - 50 Gy /25#/5wks and the study group (B) received hypofractionated RT- 42.5 Gy/16#/3wks Both protocols are biologically equivalent as calculated by TDF table. Biologically effective doses (BED) were verified by utilizing the following formula.

$$BED = TD \left(1 + \frac{d}{\alpha} / \frac{\beta}{\alpha} \right)$$

TD – total dose, d – dose per fraction
Initial work up included full blood count, kidney and liver function tests and CT chest and upper abdomen.

Patients were planned on Simulator-CT (Simulix - Nucletron) and treated on linear accelerator (Elekta-Synergy) with 6MV energy. Two tangential portals for the chest wall were planned on simulator with lung slice (central lung distance) not exceeding 2.5cm. Direct anterior field to the ipsilateral supraclavicular area. Universal bolus over chest wall was used every alternate day.

Written consent was taken before starting the treatment. Following expected toxicities of radiation along with local control and workload of the institution were compared. Acute skin reactions were categorised according to RTOG recommendations assessed weekly during RT. HRCT chest and spirometry were performed before starting radiation and at 6 months after RT. HRCT was done with 1 mm sections at 10 mm intervals with the patient in supine position and in full inspiration with reconstruction in bone algorithm and imaging at standard lung window settings on the CT scan (Siemen’s, Magnetom Avanto, 1.5 Tesla). The lung and pleural changes on the treated side were evaluated by two co-operative experienced radiologists. HRCT was used as baseline examination for each patient. The post radiation HRCT chest findings for lung toxicity, were categorized as: 1) Ground glass opacification. 2) Pleural thickening. 3) Septal lines, linear opacifications and subpleural opacities. Spirometry was done and FEV1 values were graded according to American Thoracic Society Grades for severity of a pulmonary function test abnormality. Complete blood counts were done according to the protocol before starting RT and weekly during RT. The haematological depression in any of the components were graded according to RTOG recommendations. Lymphoedema was taken as a clinical finding. The arm circumference was measured at 20 cm above and below the olecranon process of ulna. Measurements were taken before starting RT, after completion of RT and after six months of radiotherapy and were categorised as G0 (no change in circumference), G1 (0-1cm), G2 (1-2cm) and G3 (>2cm). Statistical analysis was conducted using the Statistical package for the Social Sciences (SPSS) version 16. Frequency tables with counts and percentages were used to describe pre-treatment and treatment characteristics for patients in both treatment groups. The nominal categorical characteristics between the two treatments were compared using chi-square test. For continuous variables, mean and median values were compared between the groups using the *t*-test. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

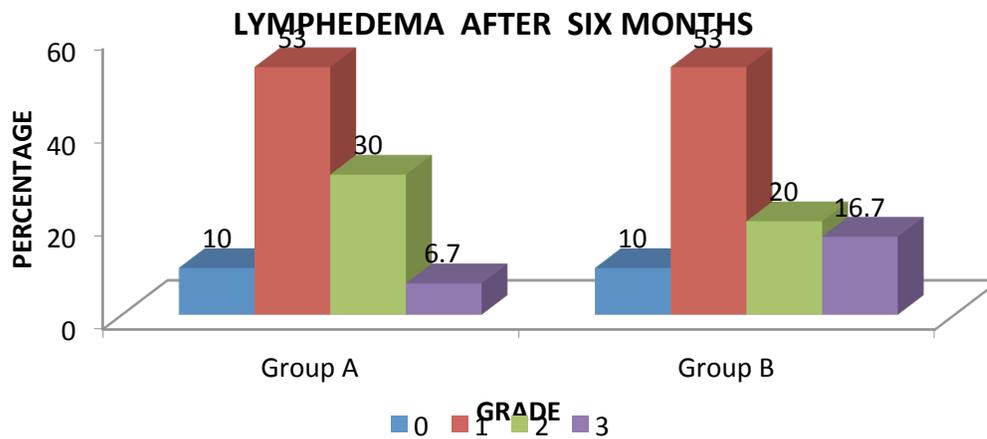
Both treatment groups were comparable in terms of age, gender, tumour stage and laterality (table 1).

Table 1: Baseline characteristics

Characteristics		Conventional group (Group A)	Hypofractionated group (Group B)	<i>p</i> value
Age	(Mean ± S.D)	48.566 ± 9.50	50.933 ± 9.464	0.322
Gender	Male	0 (0%)	2 (6.7%)	0.150
	Female	30 (100%)	28 (93.3%)	
Residence	Rural	21 (70%)	22 (73.3%)	0.774
	Urban	9 (30%)	8 (26.7%)	
Laterality	Left	15 (50%)	14 (46.7%)	0.796
	Right	15 (50%)	16 (53.3%)	
Stage	IIA	6(20%)	7 (23.3%)	0.145
	IIB	15 (50%)	7 (23.3%)	
	IIIA	7 (23.3%)	8 (26.7%)	
	IIIB	2 (6.7%)	7 (23.3%)	
	IIIC	0 (0%)	1 (3.3%)	

Table 2: Skin and Haematological Toxicity Grades 2-4

Max Toxicity	Skin Toxicity Grades 2-4		Haematological toxicity Grades 2-4	
	Group A	Group B	Group A	Group B
	Number (%)	Number (%)	Number (%)	Number (%)
2	4 (13.33%)	2 (6.7%)	6 (20.0)	3 (10.0)
3	3 (10%)	0 (0%)	1 (3.3)	0 (0.0)
4	0 (0%)	0 (0%)	0 (0.0)	0 (0.0)
Chi square	1.286		0.476	
P value	0.257		0.490	
Significance	NS		NS	



Graph 1: Graphical representation of lymphedema after 6 months of treatment in both groups

The grade 2 and 3 skin toxicity in group A was 13.33% and 10% respectively. Grade 4 toxicity was not seen. Group B had grade 2 in 6.7% patients. No patient had grade 3 and 4 toxicity in group B. The difference was not significant (p=.257) (table 2). The

haematological toxicity grade 2-4 was observed in 7 patients in group A and only 3 patients in group B but the difference was statistically insignificant (p=.490) (table 2).

Table 3: Lymphedema

Lymphedema	Group A		Group B		p value	
	Number	Mean ± S.D	Number	Mean ± S.D		
Before RT	0	30 (100.0)	.0000±.00000	30 (100.0)	.0000±.00000	-
After RT	0	24 (80.0)	0.3000 ± .65126	17 (56.7)	.4333 ± .50401	0.120 (NS)
	1	3 (10.0)		13 (43.3)		
	2	3 (10.0)		0 (0.0)		
After 6 months	0	3 (10.0)	1.3333 ± .75810	3 (10.0)	1.4333 ± .89763	0.789 (NS)
	1	16 (53.3)		16 (53.3)		
	2	9 (30.0)		6 (20.0)		
	3	2 (6.7)		5 (16.7)		

After six months of treatment, grade 0 lymphedema was seen in 10% patients, grade 1 in 53%, grade 2 in 30% and grade 3 in 6.7% patients in group A. In group B, 10%, 53%, 20% and 16.7%

respectively. This was not statistically significant (p=.789) (table 3 and graph 1).

Table 4: Spirometry FEV1

	GRADE	Group A			Group B			p value
		Number	Percentage	Mean ± S.D	Number	Percentage	Mean ± S.D	
Before RT	0	18	60.0	.5333 ± 86037	21	70.0	.3333± .54667	0.391 (NS)
	1	10	33.3		8	26.7		
	2	1	3.3		1	3.3		
	3	0	0.0		0	0.0		
	4	1	3.3		0	0.0		
After 6 months	0	8	26.7	1.3333 ± 1.12444	10	33.3	1.2000±1.0 6350	0.690 (NS)
	1	10	33.3		8	26.7		
	2	7	23.3		8	26.7		
	3	4	13.3		4	13.3		
	4	1	3.3		0	0.0		

Spirometry was performed before RT and after completion of six months. The difference in both groups was not significant

statistically (p=.391 before RT and p=.690 after six months (table 4).

Table 5: Lung toxicity in HRCT

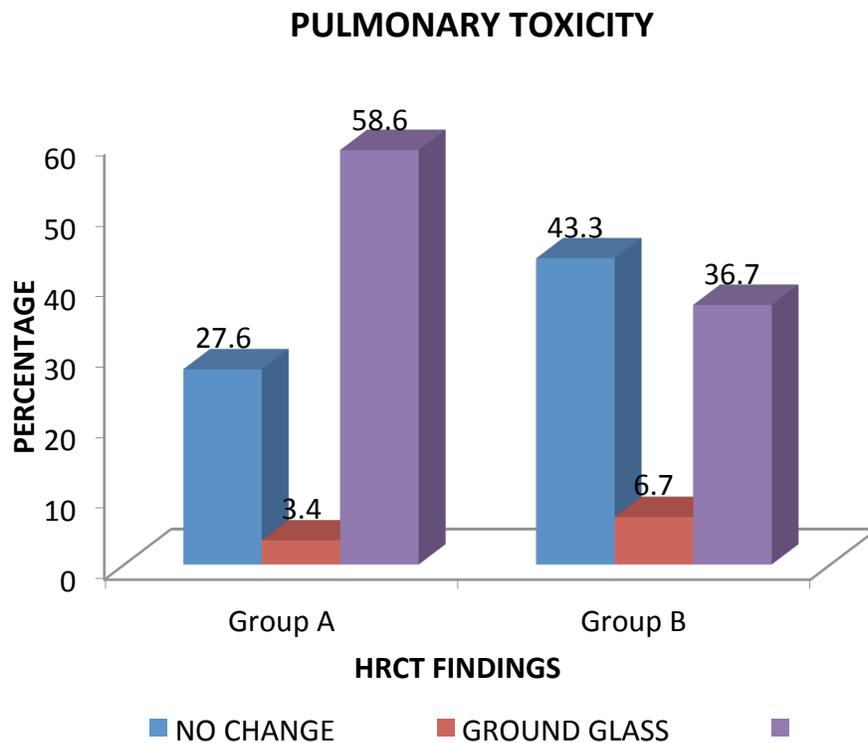
HRCT FINDINGS	Group A		Group B	
	Number	Percentage	Number	Percentage
0	8	27.6	13	43.3
1	1	3.4	2	6.7
2	3	10.4	4	13.3
3	17	58.6	11	36.7
Total	29	100.0	30	100.0
Chi Square	2.936			
P value	0.420			
Significance	NS			

Table 6: Correlation between lung toxicity and Spirometry FEV1

Groups	r value
Group A	0.292
Group B	0.174

The changes in the lung on HRCT were observed (table 5 and graph 2). In group A ground glass was seen in 3.4% patients, pleural thickness in 10.4% and septal lines, linear opacifications and subpleural opacities were seen in 58.6% patients. In group B, it was 6.7%, 13.3% and 36.7% respectively.

There were no changes observed in 27.6% patients in group A and 43.3% patients in group B. overall the difference in changes observed in both arms was not significant (p=0.420)



Graph 2: Graphical representation of lung toxicity in HRCT after 6 months

There was a correlation between lung toxicity and spirometry values in both groups (table 6), the r value for group A was 0.292 and for group B was 0.174. The use of 16 fractions (instead of 25), saves 900 treatment sessions per 100 patients (2500-1600=900). This corresponds to an additional number of 56 (900:16) patients that could be treated by the same number of fractions. Thus this cost-effective and convenient RT schedule seems to be safe and effective for selected patients.

DISCUSSION

Postoperative radiotherapy is widely used in breast cancer treatment and its value in reducing the risk of local and loco-regional recurrence is well recognised. Acute skin toxicity or radiation dermatitis is one of the important physical factors that effect on patients’ quality of life (QOL) during and shortly after radiotherapy. In the present study, hypofractionated group had grade 2 in 6.7% patients and no patient had grade 3 and 4 toxicity. Elsayed M Ali et al¹⁴ in their study had grade 2 dermatitis in 9.09% patients in conventional RT group and in 24% patients in hypofractionated RT group which was not seen in our study. El-Sayed MI et al¹⁵ in another study showed that grade 2 skin reactions were 25.3% in conventional RT group and 8.8% in hypofractionated RT group which is consistent with our study. Osaka T et al¹⁶ in their study demonstrated that grade 2 and grade 3 toxicity was 8% in 2% respectively in hypofractionated RT group and in conventional RT group it was 20% and 2% which again show that acute skin toxicity is less in hypofractionated protocols. Deantonio L et al¹⁷ in their study had grade 2 and 3

toxicity as 41% and 6% in conventional group and 22% and 2% in hypofractionated group which was significantly lower in hypofractionated group (p<0.001) although in our study the difference was not significant.

Lymphoedema is an established complication of both axillary lymph node dissection and axillary RT. Only 10% of patients never developed this problem in either group of the study. Grade 1 lymphoedema was seen in 53.3% of patients in both groups. Grade 2 and 3 was 30%,6.7% in group A and 20% and 16.7% patients respectively. it was observed that higher grade of lymphoedema was observed in more number of patients in the hypofractionated group but statistically it was not significant (p=0.789). Whelan TJ et al¹⁸ commenced a study to compare effectiveness of hypofractionated 3-week schedule of whole-breast irradiation to a 5-week schedule and revealed that after 10 years of treatment, accelerated, hypofractionated whole-breast irradiation was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes. Chua B et al¹⁹ reported 9.5% arm oedema with axillary dissection, 6.1% with radiation and 31% when two modalities were combined (p<0.001). Erickson VS et al²⁰ reported 26% lymphoedema after breast cancer treatment. Petrek JA et al²¹ in their study showed lymphoedema in the range of 6-30%. At Memorial Sloan Kettering cancer centre the experience from 1977 to 1979, based on a cohort of 20 years breast cancer survivors, measurable lymphoedema documented as 31%.²² Changes in lung capacity and volume are expected after RT since there are potential risks of damaging the pulmonary

parenchyma, losing type II pneumocytes, losing surfactant and edema in the basement membrane.²³ But there is also the possibility that the patient can remain asymptomatic or never present any changes, be it in the parenchyma or in the pulmonary function, due to the “compensation in relation to the healthy lung”, which did not receive radiation.²⁴ Dayane Evellyn dos Santos et al²⁵ in their study found that Spirometry showed a significant decrease in FVC (23.52%), FEV1 (26.23%) and PEF (10.12%), (p=0.001). The FEV1/FLC ratio did not present significant changes (p=0.430). Fragkandrea I et al²⁶ in their study concluded that there was no significant difference between the change in mean values of FVC, FEV1, and DLCO from baseline to 6 months between conventional RT group and hypofractionated RT group. Jaen J et al²⁷ investigated the long term effects of breast radiotherapy to the lung with PFTs and reported that changes in PFT values were reversible at 7 year follow up. Moreover, no correlation between dosimetric factors and spirometry changes were found in this study. Radiation-induced pulmonary changes have been investigated for conventionally fractionated schedules. Nevertheless, there is a small number of prospective studies investigating the effect of RT in lung function as assessed with the combination of HRCT and PFTs, in particularly comparing two different radiotherapy fractionation regimes.²⁸⁻³⁰

In our prospective study, the HRCT findings of the two groups of patients were comparable. Although ground glass appearance was observed in more patients in the hypofractionated arm, it was statistically non significant. Ooi GC et al³¹ reported that all their 30 patients yielded HRCT findings at three months after RT and the situation was the same up to one year^[30] Platanotis GA et al³² in their study observed postradiation changes in 15/30 patients. These lesions were evident in the ipsilateral upper lobe of the lung, which was subjacent to the radiated area.

Our study showed that there was no significant increase in toxicities in patients treated with hypofractionated protocol. Although our study had small number of patients, but the results were similar to many previous studies. The use of 16 fractions (instead of 25), saves 900 treatment sessions per 100 patients (2500-1600=900). This corresponds to an additional number of 56 (900:16) patients that could be treated by the same number of fractions. Thus this cost-effective and convenient RT schedule seems to be safe and effective for selected patients.³³ The conventional and hypofractionated radiotherapy protocols were similar in terms of locoregional control. Hypofractionated radiotherapy was cost effective and more convenient to the patients. Studies with larger sample sizes and longer follow up should be instituted for further validation of the safety of the hypofractionated radiotherapy.

CONCLUSION

The conventional and hypofractionated protocols of radiotherapy in post mastectomy patients are comparable in terms of skin and haematological toxicities. The hypofractionated protocol can be safely used as the toxicities and effectiveness are comparable to the conventional radiotherapy in post mastectomy breast cancer patients as the use of 16 fractions (instead of 25), saves 900 treatment sessions per 100 patients (2500-1600=900). This corresponds to an additional number of 56 (900:16) patients that could be treated by the same number of fractions. Thus this cost-effective and convenient RT schedule seems to be safe and effective for selected patients.

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