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A Comparative Study of Conventional and Hypo fractionated Adjuvant Radiotherapy in Post Mastectomy Breast Cancer Patients

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Abstract

Introduction: Breast carcinoma is one of the most common cancers in India accounting for 25-30% of the cancer burden. Adjuvant radiotherapy is an important part of breast cancer management. Conventional and hypofractionated radiotherapy have been seen to be equally effective and safe. *Materials & Methods:* Records of patients attending Radiotherapy OPD from january 2012 to june 2013 were analysed retrospectively. Several patient records available in the department were reviewed by census method based on pre-decided inclusion and exclusion criteria. They were analyzed and results are mentioned with the help of tables and diagrams. *Results:* Hypofractionated radiation schedule was as safe and effective as the standard 5 week fractionation schedule for the treatment of breast cancer. *Discussion:* There was no statistically significant difference between the conventional and hypofractionated arms with respect to both the locoregional and distant failure rates. There is no significant difference in either group with regard to adverse events and toxicity, including late skin toxicity. *Conclusion:* Hypofractionated radiation therapy is cheaper and more convenient for the patients and also reduces the heavy workload of already overburdened radiotherapy setup in a developing country like ours with scarcity of resources.

Keywords: Breast carcinoma, Conventional Fractionation, Hypofractionation

Introduction

Breast cancer is by far the most common cancer diagnosed in women worldwide. Breast cancer incidence has increased in most countries worldwide in the last decades.[1] Data from the International Agency for Research on Cancer (IARC) registry suggest that 45% of newly diagnosed cases of breast cancer and 55% of breast cancer related mortality currently occur in low- and middle income countries. More than 80% of Indian patients are younger than 60 years of age. In India premenopausal patients constitute about 50% of all patients (Agarwal et al., 2007). The average age of breast cancer patients has been reported to be 50-53years in various population-based studies done in different parts of the country. A significant proportion of Indian breast cancer patients are younger than 35 years of age. Young age has been associated with larger tumour size, higher number of metastatic lymph nodes, poorer tumour grade, low rates of hormone receptor-positive status, earlier and more frequent loco regional recurrences, and poorer

overall survival (Shavers, 2003; Mathew et al., 2004). There is a significant difference in the survival rates in developed and developing countries mainly because of a lack of early detection programmes and inadequate resources for treatment.

Materials and Methods

A record based descriptive study was conducted at the department of radiotherapy during the month of April, 2018. This is an analysis of 60 patients with invasive, previously untreated, non metastatic carcinoma breast that were treated by surgery, chemotherapy (neoadjuvant and/or adjuvant) and adjuvant radiation therapy. Records of patients attending Radiotherapy OPD from january 2012 to june 2013 were considered. Several patient records available in the department were reviewed by census method based on pre-decided inclusion and exclusion criteria.

All patients were treated with a continuous course of radiation therapy with once daily fractionation on Telecobalt 60. The fractionation regime was either 50 Gy in 25 fractions at 2 Gy / fraction or 42.5Gy in 16 fractions at 2.6 Gy / fraction. It was 2.6 Gy / fraction in 30/60 (50%) patients and 2 Gy / fraction in 30/60 (50%) patients. The Overall treatment time ranged from 21 to 24 (mean 22.5) days for the hypofractionated arm, while it was from 34 to 39 (mean 36.42) days in the conventional fractionation arm (p Value = 0.0001). The difference in O.T.T. was statistically extremely significant mainly in favour of the shorter treatment time of the hypofractionated arm . Statistical analysis was done using statistical tool graph pad software. Two-tailed corrected chi-square test and unpaired t-test were used for p value calculation. The results were studied on an intention-to-treat basis.

Results

Between February 2012 to June 2013, 96 breast cancer post-mastectomy patients were registered in our department for adjuvant treatment.76 patients were selected for the study. Out of them, 68 patients gave their consent and they were finally selected for this study. These patients were randomized to receive adjuvant radiotherapy according to our study protocol. 34 patients received conventional radiotherapy schedule of 50 Gy / 25 # / 5 weeks (Arm 1) and 34 patients received hypofractionated schedule of 42.5 Gy / 16 # / 3.1 weeks (Arm 2). 8 patients defaulted during the treatment course. After treatment completion patients were followed according to our study protocol. Any locoregional and distant failure was noted. Maximum duration of follow up in our patients was 15 month, minimum duration was 6 month and mean duration of follow up was 9 month. Final analysis was done on 60 patients, 30 patients in each arm. Results and observations of these patients are as follows:

Patient Related Characteristics

Table 1. No. & percentage of patients with different characteristics

1. Age distribution			
AGE GROUP	**ARM1**	**ARM2**	**P value**
20-40	10 (33.3)	11(36.7)	.15
41-60	18(60)	19(63.3)	
>60	2(6.7)	0(0)	
2. Tumour size (T)			
T	ARM1	ARM2	**P value**
T1	0	3(10)	.8165
T2	19(63.3)	12(40)	
T3	7(23.3)	11(36.7)	
T4	4(13.3)	4(13.3)	
3. Nodal status(N)			
N	ARM1	ARM2	P value
N0	13(43.3)	11(36.7)	.3568
N1	12(40)	6(20)	
N2	3(10)	8(26.7)	
N3	1(3.3)	0	
NX	1(3.3)	5(16.7)	
4. Stage			
STAGE	ARM1	ARM2	P value
1	12(40)	10(33.3)	.6554
2	7(23.3)	8(26.7)	
3	11(36.7)	11(36.7)	
4	0	1(3.3)	
5. Neoadjuvant chemotherapy status(nact)			
nact	ARM1	ARM2	
YES	15(50)	12(40)	
NO	15(50)	18(60)	
6.Response to neoadjuvant chemotherapy			
Response nact	Arm1	Arm2	P value
PR	9(60)	7(58.3)	.74
CR	4(26.7)	3(25.0)	
NR	2(13.3)	2(16.7)	

7. Hormone receptor status (ER, PR)			
ER/PR	ARM1	ARM2	P value
POSITIVE	26(86.7)	23(76.7)	.317
NEGATIVE	4(13.3)	7(23.3)	
8. hormone receptor status (Her 2/ neu)			
HER2/neu	ARM1	ARM2	P value
POSITIVE	5(16.7)	6(20)	.111
NEGATIVE	25(83.3)	24(80)	

There was no significant difference between the two regimens regarding the baseline characteristics namely; age distribution, tumour size, nodal status and Stage of the disease.

15 patients (50%) in arm 1 and 12 patients (40%) in arm 2 presented with breast cancer which was inoperable at presentation. These patients underwent 2-4 (average 3) cycles of neoadjuvant chemotherapy (CAF, CEF or taxane based) followed by surgery.

In arm1 partial response was found in 9 patients (60%), complete clinical response was found in 4 patients (26.7%) and no response was found in 2 patients (13.3%). In arm 2, partial response is found in 7 patients (58.3%), 3 patients (25%) have complete response and 2 patients (16.7%) have no response.

There was no significant difference between the two arms regarding the the number of patients in different groups of receptor status and response of neoadjuvant chemotherapy.

The acute reaction was assessed by R.T.O.G, Acute Radiation Morbidity Scoring Criteria. The late reaction was assessed by RTOG/EORTC Late Radiation Morbidity Scoring Scheme. Arm edema was assessed by taking the mid arm circumference of diseased arm and comparing it with the normal side. Arm edema>2 cm is taken as positive finding. We have assessed pulmonary toxicity on the basis of clinical evaluation, pulmonary function test, chest X-ray and occasional use of CT scan. Echocardiography performed by a single operator was used as a standard procedure for evaluating cardiotoxicity. More than 10% drop in LVEF is taken as positive finding for cardiotoxicity.

Table 2. Acute toxicity assessment

ACUTE SKIN REACTIONS(ASR)						
Arm	GRADE1	GRADE2	GRADE3	GRADE4		P value
ARM1	14(46.7)	4(13.3)	12(40)	0		.0500
ARM2	23(86.7)	1(3.3)	6(20)	0		
ACUTE ESOPHAGITIS						
esophagitis	G0	G1	G2	G3	G4	P value
Arm1	8(26.7)	9(30)	13(43.3)	0	0	.07
Arm2	16(53.3)	8(26.7)	6(20)	0	0	
ACUTE LARYNGEAL/ PHARYNGEAL TOXICITIES(l/p)						
Arm	G0	G1	G2	G3	G4	P value
Arm1	17(56.6)	8(26.7)	5(16.7)	0	0	.8407
Arm2	15(50)	10(33.3)	5(16.7)	0	0	

There was observable difference with respect to acute skin and esophageal toxicities which was not statistically significant. There was no significant difference between the two regimens regarding the number of patients with laryngeal/pharyngeal toxicity.

Table3. Late Toxicity assessment

SKIN TOXICITY			
Grade	**ARM1**	**ARM2**	**P value**
G0	**3(10)**	**1(3.3)**	**.61**
G1	**13(43.33)**	**16(53.3)**	
G2	**13(43.33)**	**11(36.7)**	
G3	**1(3.33)**	**2(6.7)**	
SUBCUTANEOUS TISSUE TOXICITY			
Grade	**Arm 1**	**Arm 2**	**P value**
GO	**2(6.6)**	**2(6.6)**	**1.00**
G1	**15(50)**	**15(50)**	
G2	**11(36.7)**	**11(36.7)**	
G3	**2(6.6)**	**2(6.6)**	
CARDIAC TOXICITY			
Arm	**Arm1**	**Arm2**	**P value**
Present	**3(10)**	**4(13.3)**	**.20**
Absent	**27(90)**	**26(86.7)**	
PULMONARY TOXICITY			
Arm	**Arm1**	**Arm2**	**P value**
Present	**4(13.3)**	**5(16.7)**	**.131**
Absent	**26(86.7)**	**25(83.3)**	
ARM EDEMA			
Arm edema	**Arm1**	**Arm2**	**P value**
present	**4(13.3)**	**6(20)**	**.480**
absent	**26(86.7)**	**24(80)**	

Chronic toxicities including skin toxicity, subcutaneous tissue toxicity, cardiac toxicity, pulmonary toxicity and arm edema were not significantly different in the two arms.

There were no cases of brachial plexopathy and rib fracture was found in our study.

Table 4.Response assessment

	No disease	**Local recurrence**	**P value**	**Distant recurrence**	**P value**
Arm 1	**29**	**0**	**.312**	**1(3.3)**	**1.96**
Arm 2	**25**	**1(3.3)**		**4(13.3)**	

In arm 2, 1 patient (3.3%) had clinically and pathologically proven chest wall recurrence. The regional axillary nodal failure was seen in none out of 60 patients**.** Distant metastasis in arm1 was found in 1 patient(3.3%) and in 4 patient(13.3%) in arm2. There was no statistically significant difference between the two arms with respect to locoregional and distant failure rates. (p=.312, 1.96).

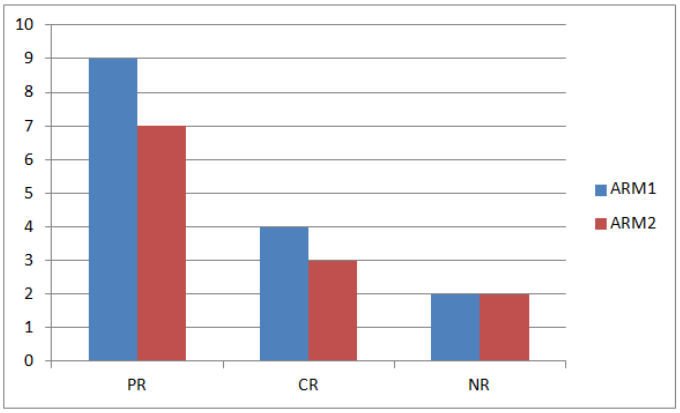

Figure 1. Response Assessment (RECIST)

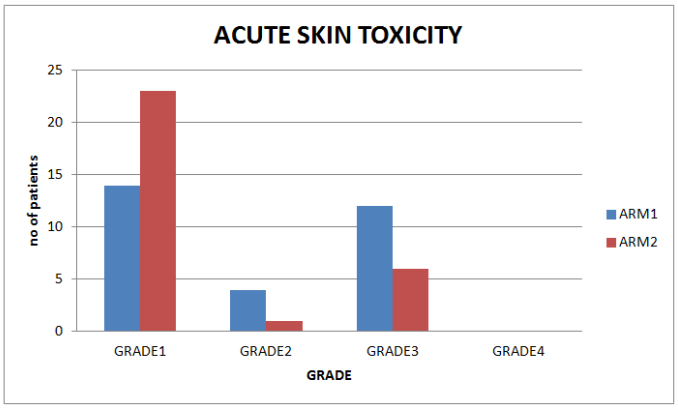

Figure 2. Acute Skin Toxicity

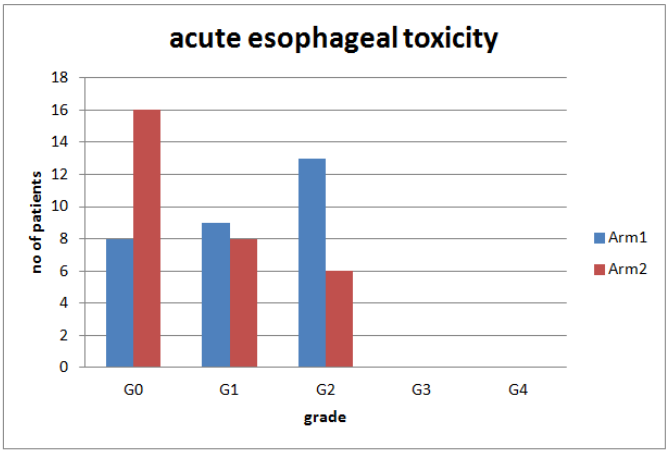

Figure 3. Acute Esophageal Toxicity

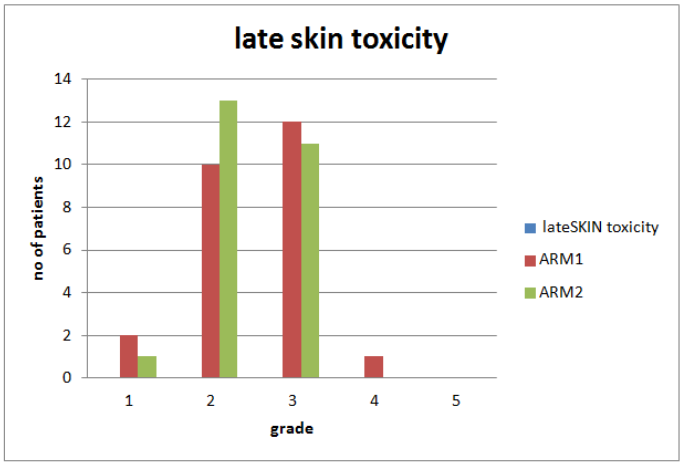

Figure 4. Late Skin Toxicity

Discussion

In this study we have compared two different dose fractionation schedules in Post Mastectomy Radiotherapy. The average age of breast cancer patients has been reported to be 50-53years in various population-based studies done in different parts of the country (National Cancer Registry Programme, 2001) In our study the most common age group affected by breast cancer in both arm1 and arm 2 was 40-60 years (60% and 63.3% respectively). This age group is in accordance with Indian data.

In our study, locally advanced disease is found in 36.7% of patients in arm1 and 40% of patients in arm2, in contrast to more than 50% as shown in many Indian studies.[2,3]

In our study, after a maximum follow up duration of 15 month (mean duration 8 month), local recurrence was found in 1patient (arm 2). There was no regional (axillary) failure in our study. Distant failure is found in 1 patient in arm1 (3.3%) and in 4 patients (13.3 %) in arm2. There was no statistically significant difference between the two arms with respect to both the locoregional and distant failure rates which is in accordance with other trials (Owen et al., 2006; Whelan et al., 2002; Dewar et al., 2007; Bates, 1988; Goel et al., 2000; Mladenovic, 2001; START A 2008 and Yamada et al., 1999).[4]

In START A, there was no statistical difference in distant relapse in either of the hypofractionated regimen compared with the control arm.[6] START B reported that the 40 Gy study arm had a statistically significant lower rate of distant relapse when compared with conventional fractionation. In Our Study diferrence in two arms (3.3% vs13.3%) is insignificant but consistent with available literature in a short follow up period available.

Three landmark trials have reported adverse events and toxicity outcomes (Canadian, START A and START B).[5,6,7] These studies reported that there was no difference in adverse events and toxicity in conventional and hypofractionation arm. There is no significant difference in either group with regard to late skin toxicity in our study.

Conclusion

Radiotherapy is an important component in management of post mastectomy breast cancer patients. Usually it is given after completion of chemotherapy with a gap of 4-6 weeks. Radiotherapy has major advantage in terms of high loco regional and distant control rate leading to improvement in disease free and overall survival. Both conventional and hypofractionated radiation therapies are comparable with respect to loco regional and distant control rates without any significant difference in

toxicities. The overall treatment time in hypofractionated radiation therapy is significantly lesser without any significant difference regarding acute and late radiation toxicities of all the normal structures included in the radiation field. It is cheaper and more convenient for the patients and also reduces the heavy workload of already overburdened radiotherapy setup in a developing country like ours with scarcity of resources.

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