VOLUME - 12, ISSUE - 02, FEBRUARY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Radiotherapy

COMPARISON OF HYPOFRACTIONATED RADIOTHERAPY WITH CONVENTIONAL FRACTIONATED RADIOPTHERAPY IN POST MASTECTOMY BREAST CARCINOMA PATIENTS: TOXICITY, EFFICACY AND FEASIBILITY STUDY

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ABSTRACT

Introduction :- Adjuvant radiotherapy plays crucial role in management of carcinoma breast patients. Altered fractionation schedules like hypofractionated radiotherapy (40 Gy/15 fractions/ 3 weeks) is time and resources saving as compared to conventional fractionation radiotherapy (50 Gy/ 25 fractions/ 5 weeks) which is time consuming. The aim of our study was to assess and compare toxicity, efficacy and feasibility of hypofractionated radiotherapy when compared with conventional fractionation radiotherapy in carcinoma breast patients. **Materials and Methods:-** The data of total 105 breast carcinoma patients was collected and evaluated in this retrospective study. This data includes socio-demographic features, tumor characteristics, treatment details and toxicity profiles of patients. Acute and chronic radiation toxicities were assessed as per RTOG common toxicity criteria for adverse events. Efficacy and toxicity data was collected at the time of completion of radiotherapy and every follow up visit from our hospital records and this data was analyzed. **Results :-** In our study, age of patients ranges from 25-83 yrs, with median age of 49.5 yrs. 42 (40 %) patients were from postmenopausal group with Stage II as predominant stage with 47 (44.76 %) patients. 51 (48.57 %) patients received conventional fractionation radiotherapy (CRT) and 54 (51.42 %) patients received hypo fractionated radiotherapy (HRT). Acute Skin Toxicity was observed in 49/51 (96.07%) patients and 45/54 (83.33%) patients in CRT and HRT group respectively. Chronic skin toxicity was observed in 18/51 (35.29%) and 16/54 (29.62 %) patients in CRT and HRT group respectively. Locoregional failure was observed in 3/51(5.88 %) and 2/54 (3.70%) patients in CRT and HRT group respectively. Toxicity and efficacy comparison in CRT and HRT group patients was statistically non significant ($p > 0.05$) **Conclusion:-** Hypofractionated radiotherapy in adjuvant treatment of carcinoma breast patients is safe, effective, feasible, compliant and time saving treatment option when compared with conventional fractionated radiotherapy.

KEYWORDS : Hypofractionated Radiotherapy, Breast Carcinoma, Post Mastectomy Radiotherapy

INTRODUCTION

Female breast cancer has now crossed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths [1, 2]. According to Globocan 2020 observatory, in India, Breast Carcinoma stands on 1st position (1,78,361 cases out of 13.24 lakhs new cases) when incidence of new cases considered for all ages and most deadliest (90,408 out of 8.51 lakhs cancer related deaths) form of cancer in 2020 [3,4].

Adjuvant Radiotherapy in Breast Carcinoma has proved to improve local control and disease free survival [5,6,7]. Most cancer treating centres are using conventional fractionation 50 Gy / 25 Fractions / 5 weeks for post mastectomy chest wall irradiation. However, some randomized trials have attracted attention towards hypofractioneted radiotherapy with dose of 40 Gy/15 Fractions /3 weeks, which proved to have similar results in terms of feasibility with comparable RT toxicity and better patient compliance. Patient compliance was better as this protocol has decreased hospital stay. Radiation oncology centres have advantage of enhanced utilization of available resources.

The aim of our study was to assess toxicity, efficacy and feasibility of hypofractionated radiotherapy when compared to conventional fractionation RT in carcinoma breast patients. Data related to post mastectomy HRT in indian set of patients is limited. This study was performed considering the fact that majority cancer centres in India have limited institutional resources and financial constraints on patients' part.

MATERIAL & METHODS

Retrospective data of 105 histopathologically proven completely treated breast cancer patients was collected from hospital records. All patients who underwent modified radical mastectomy followed by adjuvant radiotherapy (RT) with either CRT or HRT were considered for this study. All patients had received radiotherapy over Cobalt-60 teletherapy unit. 90 (85.71%) patients received RT to chest wall, axilla and supraclavicular fossa and 15 (14.28%) received RT to only chest wall. In first group, patients who received CRT with 50 Gy/25 Fr/5 weeks were included, in second group, patients who received HRT with 40 Gy / 15Fr / 3 weeks were included.

As per institutional protocol patients were reviewed on weekly basis during RT and followed up at every 3 month in 1st year and every 4 month in 2nd year of follow up. History and clinical examination was performed as per our protocol on every follow up visit. Mammogram, USG abdomen & pelvis and Chest X ray were advised at every 6 month of follow up. If symptoms were indicating local, locoregional or distant failure then additional investigations like CT scan and PET CT Scan were advised. Radiation toxicities were assessed as per RTOG Common Toxicity criteria for adverse events. All these data related to efficacy and toxicity was retrieved from hospital records. Microsoft Excel sheet was used for collection of data and data analysis.

RESULTS

As shown in Table No. 1, demographic features, the tumor characteristics in terms of clinicopathological & IHC parameters were recorded which includes age, gender, tumor stage, tumor grade, molecular subtypes on basis of hormonal receptor status (ER-Estrogen receptors/PR-Progesterone receptors/ HER), hisopathological type, status of positive axillary lymph nodes, treatment received in form of neoadjuvant and adjuvant chemotherapy, adjuvant radiotherapy, hormonal therapy.

Age of cancer patients in our study ranged from 25-83 years. The median age was 49.5 yrs. Majority of the breast cancer patients represented from 30-45 years of age group with 46 patients (43.80 %).

Table 1 : Clinicopathological and Tumor Parameters

Parameter	Group	No. of Patients (%)

Age (in yrs)	<30	1 (0.95)
	30-45	46 (43.80)
	46-60	44 (41.90)
	>60	14 (13.33)
Gender	Females	105 (100)
Menopausal Status	Premenopausal	38 (36.19)
	Postmenopausal	42 (40.)
	Perimenopausal	25 (23.80)
Stage	I	15 (14.28)
	II	47 (44.76)
	III	43 (40.95)
Lymph Node Involvement	Positive	70 (66.66)
	Negative	35 (33.33)
Histology	Ductal	97 (92.38)
	Lobular	8 (7.61)
Hormonal Receptor Status	Luminal A (ER +/PR+/HER-)	27 (25.71)
	Luminal B (ER+/PR+/Her+)	6 (5.71)
	HER2 Rich (ER-/PR-/HER +)	16 (15.23)
	Basal (ER -/PR-/HER-)	31 (29.52)
	Nonclassified	25 (23.80)
Tumor Grade	Grade I (MRBS 3-5)	2 (1.90)
	Grade II (MRBS 6-7)	31 (29.52)
	Grade III (MRBS 8-9)	72 (68.57)
Chemotherapy	Neoadjuvant Chemotherapy	51 (48.57)
	Adjuvant Chemotherapy	101(96.19)
RT	Adjuvant Radiotherapy	105 (100)
Hormonal Therapy	Tamoxifen	39 (37.14)
	AI	19 (18.09)
	No HT	47 (44.76)

40 % patients were from postmenopausal group and stage II was predominant stage with 47 patients (44.76 %). 70 patients were having positive lymph node status. Basal group was most common molecular subtype with 31 (29.52 %) patients.

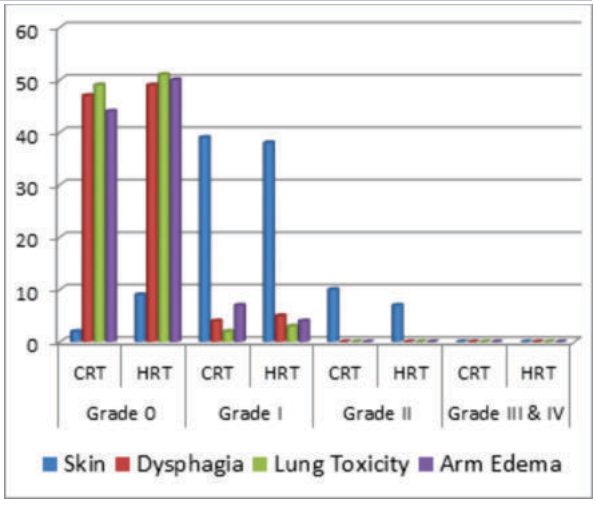
Neoadjuvant chemotherapy, adjuvant chemotherapy and hormonal therapy was received by 51 (48.57 %), 101 (96.19%) and 58 (55.23%) patients respectively.

Toxicity assessment was done at completion of radiotherapy, at every 3 month visit in 1st year and every 4 month visit in 2nd year.

Table 2 & Graph 1 show the comparison of acute toxicities in CRT vs. HRT group considered at the time of completion of radiotherapy. The skin toxicity (p = 0.085), Dysphagia (p = 0.795), Lung toxicity (p = 0.694) and arm edema (p = 0.290) were comparable and proved to be statistically non significant.

Table 2 : Acute Toxicity assessment at completion of radiotherapy

Sr. No	Toxicity (Grade)	CRT	HRT	p Value
1.	Skin Toxicity			
	Grade 0	2 (3.92)	9 (1.66)	p= 0.085
	Grade I	39 (85.18)	38 (70.37)	
	Grade II	10 (21.56)	7 (12.96)	
	Grade III	0	0	
2.	Dysphagia			
	Grade 0	47 (92.15)	49 (90.74)	p= 0.795
	Grade I	4 (7.84)	5 (9.25)	
	Grade II, III	0	0	
3.	Lung Toxicity			
	Grade 0	49 (96.07)	51 (94.44)	p= 0.694
	Grade I	2 (1.96)	3 (5.55)	
	Grade II, III	0	0	
4.	Arm Edema			
	Grade 0	44 (86.27)	50 (92.59)	p= 0.290
	Grade I	7 (3.92)	4 (1.85)	



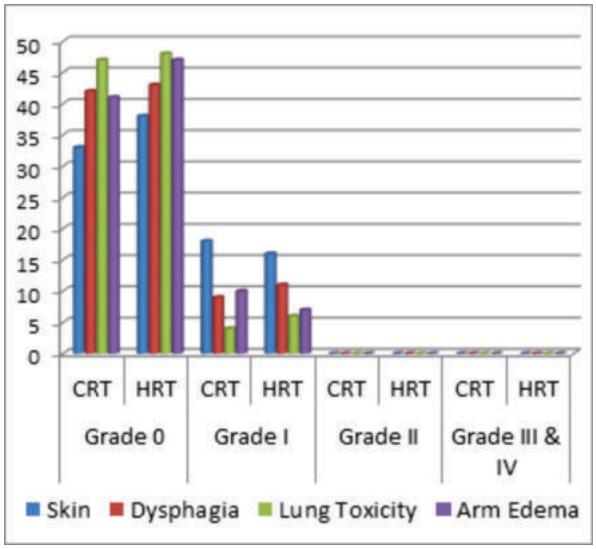
Graph 1 : Acute Toxicity (assessed at completion of Radiotherapy)

Table 3 & Graph 2 show the comparison of chronic toxicities in CRT vs. HRT group considered at the end of two year after RT.

Table 3 : Chronic Toxicity assessment at end of 2 years after RT

Sr. No	Toxicity (Grade)	CRT	HRT	p Value
1.	Skin Toxicity			
	Grade 0	33 (64.70)	38 (70.37)	p= 0.535
	Grade I	18 (35.19)	16 (29.62)	
	Grade II	0	0	
	Grade III	0	0	
2.	Dysphagia			
	Grade 0	42 (82.35)	43 (79.62)	p =0.722
	Grade I	9 (17.64)	11 (20.37)	
	Grade II, III	0	0	
3.	Lung Toxicity			
	Grade 0	47 (92.15)	48 (88.88)	p =0.568
	Grade I	4 (7.84)	6 (11.11)	
	Grade II, III	0	0	
4.	Arm Edema			
	Grade 0	41 (80.39)	47 (87.03)	p =0.355
	Grade I	10 (3.92)	7 (1.85)	

The skin toxicity (p=0.535), Dysphagia (p= 0.722), Lung toxicity (p=0.568) and Arm edema (p=0.355) were comparable and proved to be statistically non significant.

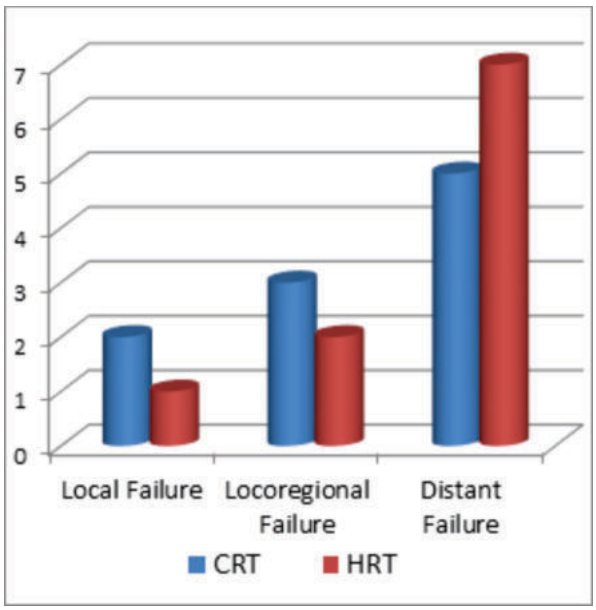


Graph 2 : Chronic Toxicity (assessed at the end of 2 year after RT)

Table 4 : Efficacy Status (assessed at the end of 2 year after RT)

	CRT No. of Patients (%)	HRT No. of Patients (%)	p value
Total Patients	51 (100 %)	54 (100 %)	p=0.965
Local Failure	2 (3.92 %)	1 (1.85 %)	
Locoregional Failure	3 (5.88 %)	2 (3.70 %)	$\chi 2$=0.069
Distant Failure	7 (13.72 %)	5 (9.25 %)	

As shown in Table 4, Efficacy assessment at the end of 2 years shows among 51 patients in 1st group who received CRT, 2 patients developed local failure in terms of recurrence in post operative bed (chest wall), 3 patients had locoregional recurrence in terms of chest wall as well as axillary lymph node recurrence. 7 patients had distant organ metastasis. 54 patients in 2nd group who received HRT, 1 patient developed local failure in terms of chest wall recurrence, 2 patients had locoregional recurrence in terms of chest wall as well as axillary lymph node recurrence. 5 patients had distant organ metastasis. (p = 0.965)



Graph 3 : Comparison of Efficacy Status (assessed at the end of 2 year after RT)

DISCUSSION

The role of adjuvant radiotherapy with conventional fractionation in post mastectomy breast carcinoma patients has been proved in many randomized trials [5,6,7]. Owen et al. conducted a prospective study, which included and randomized 1410 women with early stage invasive breast cancer who had local tumour excision to receive 50 Gy RT given in 25 fractions, 39 Gy given in 13 fractions, or 42·9 Gy given in 13 fractions, all given over 5 weeks. After a median follow-up of 9·7 years, 838 (95%) patients who survived, the risk of ipsilateral tumour relapse after 10 years was 12·1% in the 50 Gy group, 14·8% in the 39 Gy group, and 9·6% in the 42·9 Gy group ($\chi 2$ test, p=0·027) [8].

In UK START Trial A , 2236 women with early breast cancer (pT1-3a pN0-1 M0) at 17 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2·0 Gy versus 41·6 Gy or 39 Gy in 13 fractions of 3·2 Gy or 3·0 Gy over 5 weeks. After a median follow up of 5·1 years the rate of local-regional tumour relapse at 5 years was 3·6% after 50 Gy, 3·5% after 41·6 Gy, and 5·2% after 39 Gy. [9].

In UK START Trial B, 2215 women with early breast cancer (pT1-3a pN0-1 M0) at 23 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2·0 Gy over 5 weeks or 40 Gy in 15 fractions of 2·67 Gy over 3 weeks. After a median follow up of 6·0 years the rate of local-regional tumour relapse at 5 years was 2·2% in the 40 Gy group and 3·3% in the 50 Gy group.[10, 11] Precise data on lymphoedema occurrence is lacking, but the few available literature data do not report increased incidence of lymphoedema among the patients treated by HRT [11,12]. There was no difference in locoregional recurrence in either the START A or B trials and late breast changes seemed to be better with HF.

The major limitation of START A and START B trials were that in these trials the numbers of mastectomy patients were 15 % and 8 % for START A and START B respectively. In addition to this there was no direct comparison pertaining to differences in locoregional tumor relapse in Breast Conservative Surgery vs. Mastectomy patients.

Khan et. al . conducted a prospective trial where they enrolled and treated 69 patients with stage II to IIIa post mastectomy breast cancer with radiotherapy dose of 36.63 Gy in 11 fractions of 3.33 Gy over 11 days to the chest wall and the draining regional lymph nodes. After a median follow-up of 32 months, there were no grade 3 toxicities. There were 29 reported grade 2 toxicities, with grade 2 skin toxicities being the most frequent (16 of 67; 24%). There were two patients with isolated ipsilateral chest wall tumor recurrences (2 of 67; 3%). Three-year estimated local recurrence-free survival was 89.2%. The 3-year estimated distant recurrence-free survival was 90.3%.The 3-year estimated overall survival was 92.0% [13].

Large randomized controlled trials should be conducted to establish the role of hypofractionated RT in post mastectomy breast carcinoma patients, especially in indian set of patients. Hypofractionated post mastectomy radiotherapy with dose schedule of 40 Gy in 15 fractions over 3 weeks would be most convenient, feasible and cost effective option especially for patients coming from remote places for radiotherapy. This dose schedule will be resources saving option for hospitals as more breast cancer patients will be able to receive treatment on proper time over available radiation treatment units without compromising treatment outcome and with acceptable radiation toxicities.

CONCLUSION

Hypofractionated radiotherapy in post mastectomy breast carcinoma patients is effective and feasible option. Acute and chronic toxicity profile of HRT group was similar to that of CRT group. HRT is time, cost and resource saving treatment schedule with better patient compliance and hence HRT is best treatment option for high volume and low resources hospitals.

REFERENCES

1. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries Hyuna Sung, PhD1; Jacques Ferlay, MSc, ME2; Rebecca L. Siegel, MPH
2. Globocan 2020 fact Sheet
3. Globocan: Indian Cancer Observatory , 2020
4. WHO, 2020 ; GLOBOCAN 2020, 2020 Database IARC (5)
5. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337:949–55
6. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82 crandomised trial. Lancet. 1999;353:1641–48
7. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Stewart MJ, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Nat Cancer Inst. 2005;97:116-26.
8. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomized trial. Lancet Oncol. 2006;7(6):467-71.
9. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett- Lee PJ, Bliss JM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a

randomised trial. Lancet Oncol.2008;9:331–41.
10. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet.2008;371:1098–107.
11. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086–94.
12. Doré M, Cutuli B, Cellier P, Campion L, Le Blanc M. Hypofractionated irradiation in elderly patients with breast cancer after breast conserving surgery and mastectomy : Analysis of 205 cases. Radiat Oncol. 2015;10:161.
13. Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial. Khan AJet.al JCO 2017 Jun 20;35(18):2037-2043. doi: 10.1200/JCO.2016.70.7158. Epub 2017 May