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Comparison of Results Between EBRT Conventional Treatment and Hypofractionation Schedules in Breast Cancer Patients.

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Abstract

Aim: To assess efficacy of shorter fractionated Radiotherapy in post mastectomy cancer breast patients *Methods:* Inclusion Critaria– Histopathologically proven cases with Infiltrating Duct Carcinoma (IDC), Post mastectomy cases, No prior treatment (Except surgery and chemotherapy with CAF) Node Positive Cases**,**T3 & T4 Tumours**,** Positive surgical margins *Exclusion Critaria:* Metastatic-disseminated disease, Female less than 18 years and more than 70 years, Severe medical illness like heart disease, COPD, Neurological disorder. Between July 2012 to July 2014, 172 patients were included and divided into three groups, Control Group and two Study Groups. 3D-CRT Radiotherapy was given in Control Group in a dose of 50 Gy in 25# for 5 weeks. One study group received radiotherapy of 4000 cGy in 15# for 3 weeks and another study group received 4250 cGy in 16# for 3 ½ weeks. Linear Accelerator was used for the radiation treatment. Ipsilateral supraclavicular fossa (SCF) irradiation was done in patients who had more than 3 axillary nodes positive, patients who had positive supraclavicular nodes at presentation and those with inadequate axillary nodal dissection. *Results:* At 2 years, the incidence of chest wall stiffness in the study group 1 was 44.64%, in study group 2 it was 47.36% and 47.45% patients were in control group. The incidence of arm edema was 16.07% in the study group 1, 15.78% in study group 2 and 18.64% patients in control group. Local recurrence-free survival was 96.42% in the study group 1, 98.24% in study group 2 and 98.3% in the control group. Not a single patient had developed radiation pneumonitis. *Conclusion:* Shorter fractionation schedule is very much effective in preventing recurrent breast cancer and it provides a high level of patient satisfaction as well as reduced money and overall treatment time. Its shorter duration offers the added advantage of a more efficient use of resources and greater patient convenience.

Introduction

Breast cancer is the most common of all cancers and is the leading cause of cancer deaths in women worldwide, accounting for >1.6% of deaths and case fatality rates are highest in low-resource countries. A recent study of breast cancer risk in India revealed that 1 in 28 women develop breast cancer during her lifetime. This is higher in urban areas being 1 in 22 in a lifetime compared to rural areas where this risk is relatively much lower being 1 in 60 women developing breast cancer in their lifetime. The average age of the high risk group in India is 43–46 years unlike in the west where women aged 53–57 years are more prone to develop breast cancer.

Treatment of breast cancer includes surgery, chemotherapy; radiotherapy and hormonal therapy. Most of the patients are post-operative *i.e.* with post mastectomy status. Up to now no 'low risk' group has been identified where surgery alone gives adequate local control. Adjuvant radiotherapy given following surgery for primary carcinoma of the breast has been shown to reduce the incidence of locoregional recurrence from 30% to 10.5% at 20 years and breast cancer deaths by 5.4% at 20 years [6].

The first result of Canadian 12 randomized trial testing 42.5 Gy in 16 fractions against 50 Gy in 25

fractions is consistent, suggesting equivalence in terms of local control for the 16 fraction regimen. The standardization of breast Radiotherapy (START) trials were initiated by the UK coordinating committee for cancer research (now national cancer research institute) to test the effects of radiotherapy schedules using fraction size larger than 2.0 Gy. START trial A [7] tested two dose levels of 13-fractions regimens over 5 weeks in order to measure the sensitivity of normal and malignant tissues to fraction size. START Trial B [8] compares 40 Gy in 15 fractions of 2.67 Gy in 3 weeks with a control group of 50 Gy in 25 fractions over 5 weeks. Locoregional tumor relapse rates were comparable in hypofractionated arm. Any fraction size of 3.2 Gy or less as seen in both START A and B trials led to similar results in terms of local control.

The result of these trials has tremendous implications for both the patients of breast cancer and health care system. It is a known fact that prolonged daily treatments make a substantial impact on reduction of quality of life experienced by women with breast cancer, treated with radiotherapy as shown by randomized trial. Apart from quality of life benefits because of convenience and less time in the hospital, it has a tremendous logistic advantage.

Methods

This prospective observational and comparative study was undertaken in the Department of Radiotherapy & Oncology, Pravara Rural Hospital, Loni. As patients presented with locally advanced stage, they underwent modified radical mastectomy at our center .

Inclusion Critaria:

- Histopathologically proven cases.
- Post mastectomy cases.
- No prior treatment (Except surgery and chemotherapy with CAF)
- Lymph Node Positive Cases
- T_3 & T_4 Tumors
- Positive surgical margins

Exclusion Criteria:

- Metastatic, disseminated disease.
- Female less than 18 years and more than 70 years.
- Severe medical illness like heart disease, COPD, Neurological disorder.

Histopathological proven post operative cases of breast cancer patients were randomly assigned during the period from July 2012 to July 2014 .Total 172 patients included were divided into three groups, Control Group (Conventional Radiotherapy) and two Study Groups (Hypofractionated Radiotherapy).

Treatment schedule

Patients were divided into two study groups and control group which were matched on the basis of Age, Sex, ER-PR, HER2 and Menopausal status. Both Study and Control groups received six courses of CAF chemotherapy at every 21 days interval just before delivering radiotherapy. One study group received radiotherapy of 4000 cGy in 15# for 3 weeks and another study group received 4250 cGy in 16# for 3 ½ weeks. The control group received conventional radiotherapy 5000 cGy in 25# for 5 weeks. Hormonal therapy was given for 5 years in ER PR positive cases. Patients were followed on three months regular visit. Response was assessed as per WHO guidelines.

Both control and two study groups were subjected for marker CT scan thorax in the same treatment position. Then images were transferred via DICOM to treatment planning system. Segmentation of CTV and OAR were done, 3-dimensional conformal radiotherapy plan was done and approved for treatment.

Ipsilateral supraclavicular fossa (SCF) irradiation was done in patients who had more than 3 axillary nodes positive, patients who had positive supraclavicular nodes at presentation and those with inadequate axillary nodal dissection. The inferior border of supraclavicular field was at the second intercostals space, medial border was at midline and lateral border was at the anterior axillary fold or covering the medial 2 / 3rd of the clavicle. The depth of prescription ranged from D_{max} to 3 cm depending on the patients built.

Linear Accelerator was used for the radiation treatment After completion of treatment, patients were examined monthly basis, first follow up till 6 months and then 3 monthly for 2 years.

Results

From July 2012 to July 2014 (2yrs), 172 histopathologically proven cases of Invasive ductal

carcinoma of Breast were included in this study.

56 patients were assigned to receive Hypofractionated radiotherapy (Study group 1) 57 patients were assigned to receive Hypofractionated radiotherapy (Study group 2) and 59 patients were assigned to receive Conventional radiotherapy (Control group).

All groups received 6 courses of chemotherapy with CAF regime and hormonal therapy (depending upon the hormonal status).

Patients Characteristics

9% patients were in stage II and 91% were in stage III. All the patients had post-mastectomy status. Overall 35% of patients had incomplete axillary clearance both in study and control group respectively. Patients recorded in this study were maximally from rural area (90%) and most of them were in low socioeconomic status (71%).

Late radiation toxicity

Chest stiffness and arm oedema were the common side effects seen. Most of the patients tolerated radiation well & took treatment without interruption. The incidence of chest stiffness was 44.64% in the study group 1, 47.36% in study group 2 and 47.45% patients in control group. The incidence of arm edema was 16.07% in the study group 1, 15.78% in study group 2 and 18.64% patients in control group.

Patient's characteristics

		Study Group 1 (n=56)	Study Group 2 (n=56)	Control Group (n=59)
Age	Median	49	51	48
Habitat	Rural	50	51	54
	Urban	6	6	5
Stage	II	5	7	5
	III	51	50	54
Menopausal Status	Premenopausal	6	4	6
	Perimenopausal	14	17	15
	Postmenopausal	39	37	38
Surgery	MRM	35	38	37
	SM+AX	21	19	22
Hormonal Status	ER+	44	46	45
	ER-	12	11	14
	PR+	40	41	41
	PR-	16	16	18
	HER2 neu +	12	10	9
	HER2 neu -	44	47	50
Skin Reaction Grade	0	14	16	15
	1	28	28	27
	2	14	12	16
	3	0	1	1
Local Recurrence		2	1	1
Distant Metastasis		3	2	3

Local Recurrence Free Survival

Four patients experienced local breast cancer recurrence as a first event: 2 in the study group1,1 in study group 2 and 1 in the Control group. At 2 years, local recurrence-free survival was 96.42% in the study group 1, 98.24% in study group 2 and 98.3% in the control group. 6% & 8% of patients died due to metastatic disease in study & control group respectively.

Discussion

The beneficial effect of radiotherapy after surgery has been unequivocally demonstrated in randomized trials. Radiotherapy after surgery not only improves local recurrence rates but also improves survival. Conventional radiotherapy after surgery usually implies giving a dose of 50 Gy in 25 fractions, that are 2 Gy per fraction over 5 weeks.

In this regard, there has been recent interest in hypofractionation, which means giving higher dose per fraction to target area and thereby allowing a

lesser overall treatment time. A typical course of radiation therapy lasts nearly for 5–6 weeks in post-mastectomy patients. Conventionally, a dose per fraction per day of 1.8 to 2 Gy has been used in treatment of breast cancer, stemming from concern that fraction sizes of larger than 2 Gy might increase the likelihood of the late effects on healthy tissue toxicity in breast cancer patients. A number of reports of with schedules using 1.8 to 2.0 Gy per fraction have been published with 60% to 90% of patients reporting high recurrence free survival and overall survival.

Therefore, a technique which reduces the treatment time by half (3 weeks instead of the present 6 weeks) while maintaining local control rates needs to be viewed with great interest. Recent studies examining 13 to 16 fractions of hypofractionated radiation therapy (using larger dose per fraction) compared with the present 25 fractions are providing crucial supportive evidence.

In START trial B, Breast cancer patients 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. Median follow-up was 9.9 years (IQR 7.5–10.1), after which 95 patients had loco-regional relapses. The proportion of patients with locoregional relapse at 10 years did not differ significantly between the 40 Gy group (4·3%, 95% CI 3.2–5.9) and the 50 Gy group (5·5%, 95% CI 4.2–7.2; HR 0.77, 95% CI 0.51–1.16; p=0·21).

In CANADIAN Trial, Breast cancer patients were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 42.5 Gy in 16 fractions of 2.67 Gy over 3 ½ weeks. The risk of local recurrence at 10 years was 6.7% among the 612 women assigned to standard irradiation as compared with 6.2% among the 622 women assigned to the hypofractionated regimen (absolute difference, 0.5 percentage points; 95% confidence interval [CI], -2.5 to 3.5).

In this study, 172 breast cancer patients were recruited within 2 years period. In our study four patients experienced local breast cancer recurrence as a first event: 2 in the study group 1, 1 in study group 2 and 1 in the Control group. At 2 years, local recurrence-free survival was 96.42% in the study group 1, 98.24% in study group 2 and 98.3% in the control group. Not a single patient had developed radiation pneumonitis as a late complication in both study & control group respectively.

These results do suggest that the intended short 3-week schedule of radiotherapy has achieved a high level of local control.

The results of these trials have tremendous implications for both the patients of breast cancer and health care system. Apart from quality of life benefits because of convenience and less time in the hospital, it has a tremendous logistic advantage. Presently radiotherapy for breast cancer accounts for 25–30% of all radiation therapy burden. The shorter schedule also will permit more efficient use of resources, in that up to 50% more patients can be treated with existing equipments and personnel.

Summary & Conclusion

- 172 histopathologically proven cases of Invasive ductal carcinoma of Breast were included in this study
- 56 patients were assigned to receive Hypofractionated radiotherapy (Study group 1) 57 patients were assigned to receive Hypofractionated radiotherapy (Study group 2) and 59 patients were assigned to receive Conventional radiotherapy (Control group).
- Majority of the patients were in the age group of 40–60 years.
- 9% patients were in stage II and 91% were in stage III.
- Grade I skin reactions were more commonly seen in both control and study group.
- Chest stiffness and arm oedema were the common side effects seen.

Four patients experienced local breast cancer recurrence as a first event: 2 in the study.

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