Research Article

Comparison of result and outcome of conventional and hypofractionated radiotherapy in post-operative breast cancer patients

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ABSTRACT

Background: Radiotherapy following surgery is to minimize the risk of disease recurrence in carcinoma breast. Conventional fractionated radiotherapy is associated with lengthy hospitalization and longer waiting lists. However, hypofractionated radiotherapy had been studied in the western countries and associated with less overall treatment time, more convenient for patients and health-care providers, but there are no enough data in eastern India. **Aims and Objectives:** The present study was planned to compare the locoregional control and toxicity of conventional fractionated radiotherapy with hypofractionated radiotherapy in post-mastectomy early and locally advanced carcinoma breast patients of eastern India. **Materials and Methods:** The study was conducted on 108 patients with histologically proven invasive ductal carcinoma breast, and modified radical mastectomy was done. 53 patients in control group received 50 Gy in 25 fractions in 5 weeks and 55 patients in study group received hypofractionated radiotherapy 42.56 Gy in 16 fractions in 3.1 weeks. **Results:** Median age of the patient in control group was 50 years and study group was 48 years. The incidence of Grade 1 acute skin toxicity was 75.4% (40/53) and 76.3% (42/55) in patients of control group and study group, respectively. Late skin toxicity grade 1 in control group and study group was 73.6% (39/53) and 72.7% (40/55), respectively. At the end of follow-up of 2 years, the incidence of locoregional disease control in control group and study group was 90.5% (48/53) and 89% (49/55), respectively. **Conclusion:** In our study, both control group and study group showed almost similar results in terms of locoregional disease control and toxicities. Hence, hypofractionation radiotherapy is not inferior to conventional fractionation radiotherapy in terms of disease control and late toxicities.

KEY WORDS: Breast Cancer; Hypofractionation; Toxicity

INTRODUCTION

Breast cancer is the most prevalent cancer of women in worldwide. It is the most common cancer among women in both more developed and less developed countries. As per the Indian Cancer Registry, breast cancer is the leading cancer across all its Population-Based Cancer Registries (PBCRs): 26.3% in Kolkata (PBCR 2009-2011), 26.8% in Chennai and Delhi, 29.7% in Mumbai, 27.3% in Bengaluru, and 14.8% in Dibrugarh . The breast cancer risk varies with age groups; for example, the risk from birth to 39 years is 1:229 (0.44%), from age 40 to 59 years 1:24 (4.14%), from age 60 to 70 years 1:13 (7.53%), and from birth to death the probability of developing breast cancer is one in seven (13.4%).[1]

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Surgery, chemotherapy, radiotherapy, and hormonal therapy are the standard treatment of carcinoma breast. The purpose of radiation treatment following surgery is to minimize the risk of disease recurrence with as little toxicity as possible. 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.[2] With conventional fractionated radiotherapy requires lengthy hospitalization and associated with higher costs and longer waiting lists. This may create a major obstacle for patients with disabilities or those who cannot rely on their families' support. The probability of missing radiotherapy is higher with older patients and those living further away from radiotherapy center.[3-5] Hypofractionated radiotherapy 13–16 fractions in post-operative carcinoma breast would be more convenient for patients, especially those coming from remote areas to radiotherapy facilities and for health-care providers, as it would increase the turnover in radiotherapy departments. There are radiobiological reasons justifying the use of hypofractionation in breast carcinoma. The alpha/beta value for breast cancer has been estimated at 4 Gy, whereas the alfa/beta value for soft tissues of the breast is approximately 3.5 Gy.[6] Since breast cancer sensitivity to radiotherapy is similar to that of healthy tissues responding with late reactions, high fraction doses may be more efficient in destroying tumor cells. Although the hypofractionated radiotherapy had been studied in the western countries, there are no enough data about hypofractionated radiotherapy in eastern India. The purpose of this study is to evaluate locoregional disease control and treatment-related toxicities of patients treated with the hypofractionated radiotherapy compared to that with the conventional radiotherapy in eastern India.

MATERIALS AND METHODS

The study was done in the Department of Radiotherapy, Nil Ratan Sarkar Medical College and Hospital , Kolkata. Breast cancer patients of early and locally advanced stage (excluding metastatic) who had undergone mastectomy surgery registered in the Department of Radiotherapy were included in the present study. The study period was from May 2013 to April 2015 (2 years). Histopathologically proven invasive ductal carcinoma post-operative cases of breast cancer patients were randomly assigned during the period. None of the patients received previous radiotherapy and chemotherapy. A total of 108 patients included were divided into conventional EBRT as control group (number of patients - 53) and hypofractionated EBRT as study group (number of patients - 55). A detailed history was taken, clinical examination was performed, and all staging investigations were completed if they had not been performed earlier.

Both study and control groups received six cycles of FAC chemotherapy regimen (F-5 fluorouracil, A-doxorubicin, and C-cyclophosphamide) on 3 weekly basis before radiotherapy. Control group received 50 Gy in 25 fractions in 5 weeks (2 Gy/fraction) and study group received 42.56 Gy in 16 fractions in 3.1 weeks (2.66 Gy/fraction). Cobalt 60 teletherapy machine was used for the radiation treatment. Patients with modified radical mastectomy were simulated with 2 dimension technique and target volumes including chest wall and ipsilateral supraclavicular region in case of positive axillary lymph nodes. Medial and lateral tangential fields used to treat chest wall, and anteroposterior field used to treat ipsilateral supraclavicular field.

Table 1: Patients characteristics in both the groups

Characteristics	Control group *n*=53 (%)	Study group *n*=55 (%)
Age		
Mean age	50 years	48 years
Living place		
Rural	43 (81.1)	44 (80)
Urban	10 (18.9)	11 (20)
Menopausal status		
Premenopausal	26 (49.1)	29 (52.7)
Postmenopausal	27 (50.9)	26 (47.3)
Side of tumor		
Right breast	29 (54.7)	32 (58.1)
Left breast	24 (45.3)	23 (41.9)
Stage		
I	3 (5.7)	4 (7.3)
II	42 (79.2)	44 (80)
III	8 (15.1)	7 (12.7)
HR		
HR+ve	40 (75.5)	43 (78.2)
HR -ve	13 (24.5)	12 (21.8)

HR: Hormonal status

Patients were reviewed weekly during radiotherapy and at the end of radiation. Follow-up schedule was at 4 weeks following completion of radiotherapy, then at 3 months post-treatment up to 2 years. Clinical examination was done at each follow-up. Toxicity was graded according to the Radiation Therapy Oncology Group criteria, during treatment and at the follow-up visits.

RESULTS

A total of 108 histologically proven cases of invasive ductal carcinoma of breast were included in the present study, and all the patients had mastectomy status. 53 patients in control group were randomly assigned to receive conventional radiotherapy and 58 patients in study group to receive hypofractionated radiotherapy. Conventional radiotherapy was given to a dose of 50 Gy in 25 fractions over 5 weeks and hypofractionated radiotherapy was given to a dose of 42.56 Gy in 16 fractions over 3.1 weeks. Both control and study groups received six cycles of chemotherapy FAC regimen and hormonal therapy depending on the hormonal status (HR).

The mean age of the patient in control group was 50 years and study group was 48 years. Most of the patients in both

Table 2: Major toxicity - acute and late skin toxicities

Skin toxicity	Grade	Control group *n*=53 (%)	Study group *n*=55 (%)	*P* value
Acute skin toxicity	G1	40 (75.5)	42 (76.4)	0.82
	G2	11 (20.7)	12 (21.8)	
	G3	2 (3.8)	1 (1.8)	
Late skin toxicity	G1	39 (73.6)	40 (72.7)	0.91
	G2	14 (26.4)	15 (27.3)	

Table 3: Disease status at the last follow-up

Disease at the last follow-up	Control group (%)	Study group (%)	*P* value
No evidence of disease	48 (90.5)	49(89)	0 0.95
Locoregional recurrence only	3 (5.6)	3 (5.4)	
Distant metastases only	1 (1.8)	2 (3.6)	
Locoregional recurrence and distant metastasis	1 (1.8)	1 (1.8)	

groups were from rural area (control group 81.1% vs. study group 80%) and associated with low socioeconomic status. Premenopausal patients were in control group 49% and study group 52.7%, and postmenopausal patients were in control group 50.9% and study group 47.2%. Most of the patients had right-sided breast cancer in both groups (control group 54.7% vs. study group 58.1%). In control group, Stage I, II, and III patients were 5.6%, 79.2%, and 15%, respectively, and study group Stage I, II, and III patients were 7.2%, 80%, and 12.7%, respectively. In control group, HR positive and negative were 75.4% and 24.5%, respectively. In study group, HR positive and negative were 78.1% and 21.8%, respectively. The incidence of Grade 1 acute skin toxicity was 75.4% (40/53) and 76.3% (42/55) in patients of control group and study group, respectively, Grade 2 skin toxicity was 20.7% (11/53) and 21.8% (12/55), respectively, and Grade 3 toxicity was 3.7% (2/53) and 1.8% (1/55), respectively. However, acute skin toxicity in control and study groups was statistically not significant ($P = 0.82$). The incidence of acute esophageal toxicity Grade I was 41.5% (22/53) and 41.8% (23/55) in patients of control group and study group, respectively, and Grade 2 toxicity was 18.8% (10/53) and 21.8% (12/55), respectively.

Late skin toxicity Grade 1 in control group and study group was 73.5% (39/53) and 72.7% (40/55), respectively, and Grade 2 toxicity was 26.4% (14/53) and 27.7% (15/55), respectively. However, late skin toxicity in both the groups was statistically statistically not significant ($P = 0.91$). Shoulder movement restriction in control group and study group was 15% (8/53) and 18.1% (10/55), respectively. Esophageal toxicity Grade 1 in control group and study group was 18.8% (10/53) and 21.8% (12/55), respectively, and Grade 2 toxicity was 11.3% (6/53) and 14.5% (8/55), respectively. Pulmonary toxicity Grade 1 in control group and study group was 7.5% (4/53) and 10.9% (6/55), respectively. There was no Grade 2 pulmonary toxicity. Most of the patients tolerated radiation well and took treatment without interruption. Chest wall stiffness and arm edema also seen as late complications. The incidence of arm edema was greatest in those patients who had both radical axillary surgery and radiotherapy to the axilla.

At the end of follow-up, no evidence of disease in control group and study group was 90.5% (48/53) and 89% (49/55), respectively. 3 patients in both the groups (5.6% in control group and 5.4% in study group) had local recurrence only. 1 patient in control group (1.8%) and 2 patients (3.6%) in the study group had distance metastases only, and 1 patient in each group had both local recurrence and distance metastases. However, at the end of follow–up, disease status in both the groups was statistically not significant ($P = 0.95$).

DISCUSSION

Breast cancer is the most prevalent cancer of women in worldwide. It is the most common cancer among women in both more developed as well as less developed countries, and radiation therapy is an integral part of the management for a large percentage of post-mastectomy patients. The local cancer control and overall survival benefits of adjuvant radiotherapy for women with early breast cancer (EBC) have been established by a systematic review of 17 randomized trials involving more than 10,000 patients.[7] The introduction of adjuvant and neoadjuvant chemotherapy and hormone therapy regimens has significantly improved the prognosis of locally advanced breast cancer.[8-10]

In our present study, the mean age of the patient in control group was 50 years and study group was 48 years. Most of the patients in both groups were from rural area (control group 81.1% vs. study group 80%) and associated with low socioeconomic status. In control group, Stage I, II, and III patients were 5.6%, 79.2%, and 15%, respectively, and study group Stage I, II, and III patients were 7.2%, 80%, and 12.7%, respectively. In control group, HR positive and negative were 75.4% and 24.5%, respectively. In study group, HR positive and negative were 78.1% and 21.8%, respectively. The major toxicity was skin toxicity. The incidence of Grade 1 acute skin toxicity was 75.4% (40/53) and 76.3% (42/55)

in patients of control group and study group, respectively, Grade 2 skin toxicity was 20.7% (11/53) and 21.8% (12/55), respectively, and Grade 3 toxicity was 3.7% (2/53) and 1.8% (1/55), respectively. However, acute skin toxicity in control group and study group was statistically not significant (P = 0.82). The incidence of acute esophageal toxicity Grade I was 41.5% (22/53) and 41.8% (23/55) in patients of control group and study group, respectively, and Grade 2 toxicity was 18.8% (10/53) and 21.8% (12/55), respectively. Late skin toxicity Grade 1 in control group and study group was 73.5% (39/53) and 72.7% (40/55), respectively, and Grade 2 toxicity was 26.4% (14/53) and 27.7% (15/55), respectively. However, late skin toxicity in both the groups was statistically not significant (P = 0.91). Shoulder movement restriction in control group and study group was 15% (8/53) and 18.1% (10/55), respectively. Esophageal toxicity Grade 1 in control group and study group was 18.8% (10/53) and 21.8% (12/55), respectively, and Grade 2 toxicity was 11.3% (6/53) and 14.5% (8/55), respectively. Pulmonary toxicity Grade 1 in control group and study group was 7.5% (4/53) and 10.9% (6/55), respectively. There was no Grade 2 pulmonary toxicity. The incidence of arm edema was greatest in those patients who had both radical axillary surgery and radiotherapy to the axilla. At the end of follow–up, no evidence of disease in control group and study group was 90.5% (48/53) and 89% (49/55), respectively. 3 patients in both the groups (5.6% in control group and 5.4% in study group) had local recurrence only. 1 patient in control group (1.8%) and 2 patients (3.6%) in study group had distance metastases only, and 1 patient in each group had both local recurrence and distance metastases. However, at the end of follow-up, disease status in both the groups was statistically not significant (P = 0.95).

Taher *et al*., in their study, observed that hypofractionated radiation therapy offers the advantage of a more efficient and productive use of radiotherapy department resources; whether machine time, staffing of treatment units, lower expenses in addition to far better patients convenience.[11] On the other hand, hypofractionation, with larger radiation dose per fraction, increases the possibility of late normal tissue damage.[12,13] 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.[14] This is confirmed by results of many trials where hypofractionated radiotherapy protocols are as effective as the conventional radiation of 50 Gy in 25 fractions,[15,16], regardless of disease stage or type of breast surgery.[17]

Regarding a number of patients and patients' age, tumor characteristics, stages of disease, and hormonal receptor status did not much differ between conventional and hypofractionation groups in our present study. A comparative study was done on conventional radiation therapy 50 Gy in 25 fractions of 2 Gy versus 41.6 Gy or 39 Gy of 3.2 Gy or 3 Gy over 5 weeks, to see rate of locoregional tumor relapse, late normal tissue effects, and quality of life in 2236 women with EBC after primary surgery. The rate of local-regional tumor relapse was 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. Our study results in terms of locoregional failure and toxicities are similar to the results of START trials, as both the groups did not show much difference.

The results of these trials have 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 the reduction of quality of life experienced by women with breast cancer, treated with radiotherapy as shown by randomized trial.[18] Apart from the quality of life benefits because of convenience and less time in the hospital, it has a tremendous logistic advantage. At present, radiotherapy for breast cancer accounts for 25–30% of all radiation therapy burden.[19] 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.

In our study, hypofractionated radiotherapy was safe and showed acceptable toxicity. Locoregional recurrence in both the groups showed statistically not significant. Hypofractionated radiotherapy schedule would be more convenient for patients, especially those coming from remote areas to radiotherapy departments and for health-care providers, as it would increase the turnover in radiotherapy Departments. Our study has more or less similar findings to studies of those who have used same hypofractionated radiotherapy schedule for locoregional control as well as toxicity profile.

However, this study contains a small number of patients and comparatively short period of follow-up that represent major limitation for the conclusion.

CONCLUSION

In our study, both control group and study group showed almost similar results in terms of locoregional disease control, disease recurrence, and toxicities. With conventional fractionation modality requires lengthy hospitalization or commuting to hospital for radiotherapy. This may create a major obstacle for patients with disabilities or those who cannot rely on their families' support and probability of missing radiotherapy is higher with older patients and those living farther away from radiotherapy centre. 5 weeks' radiotherapy in conventional fractionation is also associated with higher costs and longer waiting lists, whereas hypofractionated schedules, with radiobiological advantage of short overall treatment time, have shown same response in terms of tumor control and late normal tissue effects with the advantage of decreased workload, increased compliance, and reduced cost of treatment. Hence, hypofractionated radiotherapy is not inferior to conventional fractionation

radiotherapy in terms of disease control and late toxicities. However, whether this ultimately transforms into comparable overall survival and disease free survival needs to be tested with multi-institutional randomized study with large number of patients and with longer follow-up.

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