Original Research Article

Hypofractionated radiotherapy in post mastectomy locally advanced breast cancer: a study from a regional cancer center in North East India

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ABSTRACT

Background: Adjuvant radiotherapy has increased local-regional and overall survival rates in breast cancer. Conventional fractionation delivering 50-60 Gray (Gy) over 5-6 weeks is a standard approach. A shorter duration of hypofractionated treatment will be more convenient for patients and treatment providers if found safe and equally effective.

Methods: Around 50 high risk breast cancer patients who underwent mastectomy were enrolled and randomized into the study arms- CF (Conventional Fractionation) Arm (50Gy/25 Fr @ 2 Gy/fraction/day 5 days a week over 5 weeks) and HF (Hypo-Fractionation) arm (40.05 Gy/15 Fr @ 2.67 Gy/fraction/day 5 days a week over 5 weeks). Treatment related acute and late toxicities, loco-regional recurrence; distant metastasis and survival rates were recorded for comparison.

Results: Twenty-five patients were enrolled in each arm with baseline characters well matched. At median follow up of 44 months, OS was 80% in HF arm against 64% in CF arm (p-value: 0.292). HF arm also showed better DFS at 4 years of 76% compared to 64% in CF arm (p-value: 0.411). Although the difference was not significant statistically, the Hazard Ratio of 1.543 (95% CI: 0.549-4.339) for DFS and 1.801 (95% CI: 0.603-5.377) for OS indicated trends towards better outcomes in HF arm in terms of disease control and survival. Acute and late toxicities were also lesser in HF arm, though not statistically significant (all p-values >0.05).

Conclusions: In post mastectomy setting, HFRT is comparable to CFRT in terms of safety and efficacy, will be more convenient for patients and care givers and hence can be a routine standard practice.

Keywords: Breast cancer, Hypofractionation, Post-mastectomy, Radiotherapy

INTRODUCTION

Breast cancer is the most common malignancy in females worldwide and multi-modality treatment is required to cure this dreaded disease. Radiotherapy has an important role in breast cancer treatment, as established from the landmark studies of the British Columbia Cancer Agency, Danish Breast Cancer Cooperative Group, and the Early Breast Cancer Trialists’ Collaborative Group. Addition of loco-regional radiotherapy to surgery in breast cancer...
not only improves local control and disease free survival but also has an impact on improving overall survival.

Radiotherapy in breast cancer has undergone paradigm changes with anterior photon beams in early days to tangential beams and then to modern conformal radiotherapy treatment techniques in current era. Traditionally 50 Gray in 25 fractions is a standard radiotherapy protocol for post mastectomy patients. Results of trials from Whelan et al, Owen et al and START Trialists groups, in early breast cancer have established that α/β values in breast cancer is really low and similar to that of normal tissues. They have also proved HF to be equally effective with less toxicity compared to CF in patients with early breast cancer.

Implementation of such shorter HF schedules in routine clinical practice is convenient for both patients and radiotherapy establishments in resource constrained regions like ours. Hence, there is a need to evaluate safety and efficacy of HF in our patients. However, unlike west, most of the cases in India and especially our part of country present at an advanced stage, which are not amenable to breast conservation approaches and mostly undergo mastectomy. Whether, hypofractionation can be applied routinely for post-mastectomy breast cancer patients remains debatable owing to paucity of large, prospective trials and supporting level I evidence.

With this background, this study was undertaken among the locally advanced breast cancer patients that underwent mastectomy and required adjuvant loco-regional radiotherapy. In this report, we analyze the loco-regional control, disease free survival (DFS), overall survival (OS) rates and late toxicities of therapy in such patients treated at our center with conventional versus hypofractionated radiotherapy.

METHODS

This study was carried out in Department of Radiation Oncology at Dr. Bhubaneswar Borooah Cancer Institute, Guwahati – a Regional Cancer Center located in the North Eastern region of India. The study was approved by Institutional Ethics Committee (IEC) and performed in accordance with the principles embodied in the Declaration of Helsinki. The study has been registered retrospectively with the Clinical Trial Registry-India vide registration no. CTRI/2018/04/013174.

Inclusion criteria

Female patients with histologically confirmed invasive breast cancer, who underwent modified radical mastectomy and planned for adjuvant radiotherapy as per Institutional Tumour Board decision, were eligible for study. Patients with age >18 years, tumours with pathological stage IIA-IIIC, or any patient who had received neoadjuvant chemotherapy with normal haematological, cardiac and pulmonary functions prior to radiotherapy were considered for accrual.

Exclusion criteria

Patients with tangential beam margins separation more than 22 cm were excluded. Patients with non-epithelial malignancies, those with co-existent or previous history of other malignancy, those who received prior radiotherapy to chest wall region and those with severe physical or mental co-morbidities were excluded from the study.

Study procedure

After informed consent patients were enrolled and randomized between the two arms i.e. Study Arm A- Hypo Fractionation (HF) and Control Arm B- Conventional Fractionation (CF). Patients in the HF arm received 2.67 Gray (Gy) per fraction per day to a dose of 40.05 Gy in 15 fractions, 5 days a week over 3 weeks while those in CF arm received 2 Gy per fraction per day to a dose of 50 Gy in 25 fractions, 5 days a week over 5 weeks.

Radiotherapy procedure

All patients were planned with two-dimensional conventional simulator. The clinical field borders were placed keeping in mind the adequate coverage of the chest wall and tumor bed region with radiotherapy. Care was taken to include the mastectomy scars within the treatment volume and central lung distance (CLD) within 2.5 cm. Radiotherapy was delivered using two parallel opposed tangential beams with the patient lying supine on a Breast Board. The chest wall contour was replicated and transferred to a digitizer in the treatment planning system to calculate the depth of prescription and check for adequate coverage and homogeneity.

When indicated, a separate direct anterior field was used to treat the axilla and supracavicular region with a gap junction of 0.5 cm from the chest wall field to prevent overlapping of field borders. The superior divergence of tangential fields was accounted for by using appropriate couch rotation and collimation. No separate fields for internal mammary nodes or posterior axillary boost was employed in any of the patients. All patients were treated using 6 Mega Voltage (MV) photons on a linear accelerator.

Study objectives

The objective was to compare effectiveness of the two arms by evaluating Overall Survival (OS) and Disease Free Survival (DFS) rates. Loco-regional failures and Breast Cancer related deaths were analyzed and compared between the two arms. Toxicities were graded using the RTOG/EORTC acute and late radiation morbidity scoring criteria.
Data collection and statistical analysis

All study parameters were recorded and analysed using SPSS (version 17) and GraphPad Prism softwares. Appropriate statistical tests were used for analysis of categorical and continuous data. Kaplan-Meier curves were used for survival analysis and the results compared by Log-rank test. Where appropriate, 95% confidence interval (CI) was computed and p-value <0.05 was considered statistically significant. Hazard ratios (HR) were calculated using Cox proportional hazards regression.

RESULTS

From June 2014-May 2015, 62 patients were assessed for eligibility for accrual into the study based on the inclusion and exclusion criteria stated above. Fifty patients of breast cancer who were planned for Post Mastectomy Radiotherapy (PMRT) were eventually accrued and randomized between the two arms.

| Table 1: Comparison of baseline characteristics between the study arms. |
|---------------------------------------------------------------|
| **Age (in years)** | **HF Arm (A), N= 25** | **CF Arm (B), N= 25** | **p value** |
| Mean (SD) | 43.04 (9.08) | 48.56 (10.34) | 0.05 (NS) |
| Median (range) | 43 (27-60) | 47 (32-70) | 0.77 (NS) |
| **Menstrual status** | | | |
| Premenopausal | 14 (56%) | 12 (48%) | |
| Postmenopausal | 11 (44%) | 13 (52%) | |
| **Clinical stage** | | | |
| IIA | 5 (20%) | 4 (16%) | |
| IIB | 10 (40%) | 9 (36%) | 0.95(NS) |
| IIIA | 7 (28%) | 8 (32%) | |
| IIB | 3 (12%) | 4 (16%) | |
| **Histopathology** | | | |
| Infiltrating Duct Ca | 25(100%) | 23 (92%) | 0.49(NS) |
| Other | 0 | 2 (8%) | |
| **Estrogen and progesterone receptor** | | | |
| Positive | 14 (56%) | 16 (64%) | 0.77(NS) |
| Negative | 11 (44%) | 9 (36%) | |
| **Her 2 neu expression** | | | |
| Positive | 7 (28%) | 8 (32%) | 1.0(NS) |
| Negative | 18 (72%) | 17 (68%) | |
| **Chemotherapy** | | | |
| None | 1 (4%) | 0 | |
| Neo-Adjuvant only | 4 (16%) | 6 (24%) | 0.40(NS) |
| Neo-Adjuvant → Adjuvant | 3 (12%) | 6 (24%) | |
| Adjuvant only | 17 (68%) | 13 (52%) | |
| **Hormonal Therapy** | | | |
| None | 10 (40%) | 9 (36%) | 0.94(NS) |
| Tamoxifen | 7 (28%) | 8 (32%) | |
| Aromatase Inhibitors | 8 (32%) | 8 (32%) | |

Patient, tumour and systemic therapy characteristics

The baseline characteristics of the study population between the two arms are shown in Table 1. The mean age of patients in the HF arm was slightly higher than that of the CF arm (48.56 vs 43.04 years). All patients in the HF arm had infiltrating duct carcinoma (IDC) while in the CF arm 2 patients had mucinous carcinoma histology. The clinical stage of disease (from IIA up to IIIB) was found evenly matched between the two arms. The CF arm had more number of patients with hormone receptor positivity (64% vs 56%). With regards to systemic therapy, it was seen that only one patient in HF arm did not receive chemotherapy, while all other patients across both the arms, received some form of combination chemotherapy. Fifty-two percent patients in HF arm and 56% in CF arm received taxanes. Chemotherapy was delivered mostly in the adjuvant setting and equal proportion of patients received hormonal therapy in both the arms. Statistical analysis of these data revealed no significance (all p-values >0.05) and thus showed homogeneity between the two arms.
Radiotherapy characteristics

Between the patients of the two arms HF and CF, the mean chest wall separation (18.28cm vs 18.64cm, respectively) and the average central lung distance (1.82cm vs 1.84cm, respectively) were found to be comparable (Table 2). The proportion of patients in the two arms receiving radiotherapy to nodal regions (76% in HF and 84% in CF) was also similar (p-value = 0.73).

Table 2: Comparison of radiotherapy characteristics between the two arms.

|                      | HF Arm (A) | CF Arm (B) | p value |
|----------------------|------------|------------|---------|
| Chest Wall separation (in cm) |            |            |         |
| Mean (SD)            | 18.28 (1.77) | 18.64 (1.99) | 0.50    |
| Median (Range)       | 18 (16-22)  | 18 (15-22)  | (NS)    |
| Central lung distance (in cm) |            |            |         |
| Mean (SD)            | 1.82 (0.5752) | 1.84 (0.5346) | 0.90    |
| Median (Range)       | 2.0 (1.0-2.5) | 2.0 (1.0-2.5) | (NS)    |
| Radiotherapy to SCF/axilla |            |            |         |
| Yes                  | 19 (76%)   | 21 (84%)   | 0.73    |
| No                   | 6 (24%)    | 4 (16%)    | (NS)    |

Toxicity profile

Late toxicities evident were chronic pain (local), skin changes, subcutaneous fibrosis and lymphedema of the arm. Late skin changes in the irradiated areas, which included pigmentation and mild atrophy (Grade 1) was 40% in CF arm compared to 32% in HF arm. Also, a small proportion of patients (20% in CF and 16% in HF) complained of mild to moderate pain in the irradiated area. Subcutaneous fibrosis Grade 1 was visible in 24% in CF arm and 20% in HF arm, while Grade 2 fibrosis occurred in 12% and 8%, respectively. Incidence of lymphedema was also higher in CF arm (28% versus 16%).

Table 3: Comparison of radiotherapy induced late toxicities between the two arms.

|                      | HF Arm (A), N= 25 | CF Arm (B), N= 25 | p value |
|----------------------|-------------------|-------------------|---------|
| Chronic pain         |                   |                   |         |
| Yes                  | 4 (16%)           | 5 (20%)           | 1.00    |
| No                   | 21 (84%)          | 20 (80%)          | (NS)    |
| Skin changes         |                   |                   |         |
| Yes (Grade 1)        | 8 (32%)           | 10 (40%)          | 0.77    |
| No                   | 17 (68%)          | 15 (60%)          | (NS)    |
| Subcutaneous fibrosis|                   |                   |         |
| Grade 0 (None)       | 18 (72%)          | 16 (64%)          |         |
| Grade 1              | 5 (20%)           | 6 (24%)           | 0.76    |
| Grade 2              | 2 (8%)            | 3 (12%)           | (NS)    |
| Lymphedema           |                   |                   |         |
| Yes                  | 4 (16%)           | 7 (28%)           | 0.49    |
| No                   | 21 (84%)          | 18 (72%)          | (NS)    |

All the late toxicities that occurred were comparable between the two arms (p-values >0.05) while there was no incidence of radiation pneumonitis, brachial plexopathy or cardiac sequelae in any patient of either arm at the time of last follow up (Table 3).

Recurrence and survival pattern

At a median follow up of 44 months (range: 17-51 months), the overall incidence of loco-regional failure was 8%, distant metastasis was 30% and breast cancer related death was 28% for the study population. The Overall Survival was 72% and the 4-year Disease Free Survival was 70% across both arms.
Patients in HF arm fared better than those in CF arm in terms of local recurrence (4% vs. 12%), distant metastasis (24% vs. 36%) and death from breast cancer (20% vs. 36%). Patients in HF arm had better OS with 80% against 64% in CF arm (p-value: 0.292) (Figure 1). HF arm also showed better DFS at 4 years with 76% when compared to 64% in CF arm (p-value: 0.411) (Figure 2).

Although the difference was not significant statistically, the Hazard Ratio of 1.543 (95% CI: 0.549-4.339) for DFS and 1.801 for OS (95% CI: 0.603-5.377) between the two arms clearly indicate that HF was superior to CF in terms of disease control and survival in our study.

The 10 year follow up results of the START Trials A and B have shown that the local-regional relapse did not differ significantly between conventional fractionation and any of the hypofractionated regimens evaluated.11 But the normal tissue effects like breast shrinkage, edema and telengiectasia were significantly less in the hypofractionated arms. Thus, hypofractionated radiotherapy has become the standard of care for early stage breast cancer patients in Canada, UK and most parts of Europe.

However, the observations of the START Trials need to be extrapolated with caution in our patients, because these trials were done on early stage breast cancer patients and only 15% patients in START A and 8% in START B underwent mastectomy. Thus, there is need to evaluate hypofractionation for PMRT in locally advanced breast cancer and not many randomized controlled trials are available in this regard.

A retrospective analysis of 343 patients receiving PMRT in Egypt by Elsayed et al, showed significantly superior 4-year DFS and lesser skin toxicities in the hypofractionated arm (42.5 Gy/16 fractions).14 Pinitpatcharalert A et al, reported significant increase in 5-year OS among the patients receiving HFRT (2.65 Gy x 16-18 fractions) with no difference in toxicities, in his retrospective study of 215 patients.15 Ko et al, analyzed retrospective data of 133 PMRT patients in Christchurch Hospital, New Zealand and reported high local control rate (97.6%) and less toxicities with HFRT (40 Gy/16 fractions).16

Elsayed et al, published another prospective trial of 47 patients receiving PMRT with conventional versus hypofractionation (42.72 Gy/16F).17 The results were equivalent in terms of OS, DFS and adverse effects and observed HFRT to be advantageous in terms of reduced workload and cost of treatment. Another prospective Phase II trial on postmastectomy HFRT was reported by Khan AJ et al, where a hypofractionated regimen of 36.63 Gy in 11 fractions (3.33 Gy per fraction) over 15 days was delivered, followed by an optional mastectomy scar boost of four fractions of 3.33 Gy.18 They too reported high local control with low toxicities among the study subjects and based on the results a cooperative group phase III prospective, randomized trial of conventional versus hypofractionated PMRT has been initiated by them. In the Annual Meeting of ASTRO 2017, Sun et al.19 from China reported the 5-year results of a randomized phase III non-inferiority trial comparing HFRT and CFRT following mastectomy in 820 high risk breast cancer patients. With a median follow up of 53 months, this trial demonstrated significantly less acute Grade 3 reactions in HFRT arm (p-value 0.008) with no difference in late toxicities, 5-year local control, distant metastasis, DFS and OS. Till date, this is the only large, well-conducted randomized trial to conclusively demonstrate that HFRT to chest wall and nodal regions of

**DISCUSSION**

Postmastectomy adjuvant radiotherapy improves locoregional control and overall survival in breast cancer and the trend now a days is to deliver this treatment in hypofractionation, at least in early stage breast cancers. The evidence for hypofractionated radiotherapy in breast cancer comes mainly from four large RCTs viz. Whelan et al, Owen et al and the START Trials A and B.7,10

Whelan et al, compared 42.5 Gy in 16 fractions versus conventional radiotherapy and found equal local control and cosmesis at 10 years. Owen et al, compared 50 Gy/25 fractions against 39Gy/13 fractions and 42.9 Gy/13 fractions and concluded that breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues and hence radiotherapy can be greatly simplified by hypofractionation without compromising effectiveness or safety, and possibly improving both.7,8

![Figure 3: Consort diagram.](image-url)
breast cancer is safe and effective in the postmastectomy setting.

Our study is a single institution, hospital based, prospective, randomised trial evaluating HFRT versus CFRT following mastectomy, in intermediate-high risk breast cancer patients. The HF regimen of 40 Gy in 15 fractions (2.67 Gy per fraction) over 3 weeks, matched the study arm of START B trial and had a biologically equivalent dose (BED) similar to conventional fractionation.\textsuperscript{10} Also, our baseline study characteristics were quite comparable to those of Elsayed et al and Sun et al.\textsuperscript{17,19}

This study results favour the HFRT arm in both safety and effectiveness, albeit without statistical significance. Late toxicities like skin changes, chronic pain, fibrosis and lymphedema were comparable between the arms (p-value >0.05). These findings are in agreement with that reported by Pinitpatcharalert A et al, Elsayed et al and Sun et al.\textsuperscript{15,17,19} The HFRT arm fared better than CFRT with improved OS (80% vs. 64%, HR=1.801, p-value: 0.282) and 4-year DFS (72% vs 64%, HR=1.543, p-value: 0.405). There was less incidence of loco-regional, distant failure and death from breast cancer related events in the HFRT than the CFRT arm, although it was statistically not significant. These results are also in concordance with Elsayed et al and Sun et al, who have reported similar findings on survival and disease control in their trials.\textsuperscript{17,19} This results confirm that hypofractionation in postmastectomy radiotherapy is equally effective and safe when compared to conventional fractionation.

Limitations of our study are the relatively less number of patients evaluated and a comparatively shorter follow up. But nevertheless, it is one of the few prospective, randomized trials available in literature, evaluating the feasibility, safety and outcomes of hypofractionated radiotherapy in post mastectomy patients. There is further scope for evaluating it in multicenter phase III trials with longer follow up.

CONCLUSION

HFRT in postmastectomy patients is safe and equally effective compared to CFRT. A shorter duration of treatment is also more convenient economically and logistically, and hence there is further value for HFRT to be used in routine clinical practice for breast cancer.

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