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Original Article

# Conventional Radiotherapy with Hypofractionated Radiotherapy in Post-Mastectomy Breast Cancer Patients: A Prospective Comparative Study

**S Vijayakumar**

Associate Professor, Department of Radiotherapy, Thanjavur Medical College Hospital, Thanjavur, Tamil Nadu, India

## Abstract

**Aim:** The aim of this study is to assess the efficacy, toxicity, and feasibility of hypofractionated radiotherapy in post-mastectomy breast cancer patients compared with conventional radiotherapy.

**Materials and Methods:** A total of 80 post-mastectomy breast cancer patients were randomized into two groups for adjuvant radiotherapy. Control group of 40 patients received conventional radiotherapy of 50 GY in 5 weeks. Study group of 40 patients received hypofractionated radiotherapy of 42.72 GY in 3.1 weeks.

**Results:** The statistical analysis of the study was performed in terms of tolerability, radiation toxicities, and feasibility of the hypofractionated radiotherapy over conventional radiotherapy. There was found to be no significant difference between the two groups.

**Conclusion:** In breast cancer patients after post-mastectomy, hypofractionated radiotherapy in comparison to conventional radiotherapy finds comparable outcomes without any significant difference in radiation-induced toxicities.

**Key words:** Carcinoma breast, Hypofractionated radiotherakpy, Post-mastectomy radiotherapy, Toxicities

## INTRODUCTION

Carcinoma breast being the most common cancer in females usually presents as a locally advanced disease which makes the treating oncologist difficult in taking treatment decisions.[1,2] Hence, radical mastectomy is more often performed than breast conservative surgeries such as lumpectomy, quadrantectomy in developing countries like India, where people do not give much importance to cosmetic outlook.[3,4] Nearly, all of these post-mastectomy patients require adjuvant radiotherapy to prevent locoregional recurrence and distant metastasis.[5-7]

For long, conventional radiotherapy is being delivered to the chest wall and drainage area. In the recent past, most of the centers are trying various methods of delivering different types of fractionations in the adjuvant radiotherapy.[8,9] The most tested regimen of adjuvant radiotherapy in carcinoma breast is hypofractionated radiotherapy with a total dose of 42.72 GY, 2.67 GY per fraction in 16 fractions. The other fractionation protocols are 42.9 GY in 13 fractions, 39 GY in 13 fractions, 40 GY in 15 fractions, 28.5 GY in 5 fractions, and 30 GY in 5 fractions.[10-13]

In this study, we compare conventional fractionation 50 GY, 200 CGY per fraction, 5 fractions per week, 25 fractions in 5 weeks, with the hypofractionation regimen 42.72 GY, 2.67 GY per fraction, 5 fractions per week, and 16 fractions in 3.1 weeks. Post-operative radiotherapy is aimed at eradicating subclinical disease, superior locoregional control, and acceptable risk of normal tissue reactions, for example, lungs and heart.[14,15] Post-mastectomy radiotherapy is indicated in patients with 1–3 positive axillary lymph nodes and tumor size equal to or more than 5 cm or positive/unknown pathological margins.[16] Conventional fractionation modality requires a lengthy hospitalization or commuting to the hospital

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**Corresponding Author:** Dr. S Vijayakumar, Department of Radiotherapy, Thanjavur Medical College Hospital, Thanjavur - 613 004, Tamil Nadu, India.

for radiotherapy for a prolonged period. The probability of missing radiotherapy is higher with older patients and those living farther away from radiotherapy centers. This also applies to patients with disabilities or those who cannot rely on their families support.[17,18]

Hypofractionation is a strategy allowing shortening the time of radiotherapy. Hypofractionated radiotherapy is gaining momentum, which delivers a higher dose per fractions for a biologically equivalent dose while maintaining the same toxicity and locoregional control.[2,10] Hypofractionated regimen for post-operative breast cancer is also radiobiologically justified. Since the sensitivity of breast cancer to radiotherapy is similar to that of healthy tissues responding with late reactions, high fraction doses may be more efficient in destroying tumor cells.[2]

### Aim

The aim of this study is to assess the efficacy, toxicity, and feasibility of hypofractionated radiotherapy in post-mastectomy breast cancer patients compared with conventional radiotherapy.

## MATERIALS AND METHODS

This prospective study was carried out in the Department of Radiotherapy, Thanjavur Medical College Hospital from June 2018 to May 2019. Post-mastectomy patients were randomized into two groups – the control group and study group with 40 patients in each group: Control group – Arm A – 40 patients, conventional fractionation radiotherapy regime, 5000 CGY, 200 CGY per fraction, 5 fractions per week, and totally 25 fractions in 5 weeks.

Study group – Arm B – 40 patients, hypofractionated radiotherapy regime, 4272 CGY, 267 CGY per fraction, 5 fractions per week, and totally 16 fractions in 3.1 weeks.

All patients should have undergone modified radical mastectomy with axillary node dissection followed by chemotherapy with or without hormonal therapy. Moreover, the patients should present for adjuvant radiotherapy within 1 month of the last cycle of chemotherapy. The other inclusion criteria were as follows:

1. Histological proof of breast cancer
2. Age 30–60 years
3. Pathological stage T2/T3 No/N1/Mo
4. Tumor size ≥5 cm
5. Axillary node positive
6. ECOG performance status 0–2
7. Written consent of the patient
8. Unilateral breast cancer
9. Estrogen/progesterone receptor Positive/Negative
10. Her 2 Negative.

### Exclusion Criteria

1. History of previous irradiation
2. Recurrent breast cancer
3. Active systemic lupus or scleroderma
4. Comorbid conditions such as cardiac disease, diabetes mellitus, hypertension
5. Pregnancy
6. Breast conservation surgery such as lumpectomy and quadrantectomy
7. Evidence of metastasis.

### Preradiotherapy Examination of Patients

Before the execution of radiotherapy, all the patients were evaluated with:

1. Complete clinical examination
2. Detailed cardiac evaluation
3. Thoracic medicine opinion
4. Blood test and HIV
5. CT scan chest
6. CT scan abdomen.

### Radiotherapy

In Arm A of control group, 40 patients of conventional fractionation regimen were given a total dose of 50 Gy/2Gy/per fraction/5 days a week/25 fractions/in 5 weeks. In Arm B of the study group, 40 patients of hypofractionated radiotherapy were given a total dose of 42.72 GY/2.67 GY/per fraction/5 days a week/16 fractions/in 3.1 weeks. The patients were delivered radiation in telecobalt machine to the chest wall and drainage area. The chest wall received radiation with bilateral tangential fields [Table 1].

### Monitoring of Patients during Radiotherapy

Patients on radiation treatment are regularly examined for:

1. Tolerance
2. Maintenance of general condition
3. Acute toxicities
4. Dysphagia and oral intake
5. Pulmonary symptoms
6. Cardiac symptoms
7. Arm edema
8. Appearance of metastasis
9. Psychological status.

### Follow-up

After completion of treatment, patients were advised for strict follow-up which included:

1. Routine clinical examination monthly
2. Chest radiography every month
3. Mammography every 3 months
4. Ultrasonogram of the abdomen every year
5. Bone scan whenever necessary.

## RESULTS

Going to the statistical analysis of our study, the follow-up period of patients ranged from 3 to 14 months. All patients tolerated radiotherapy well and completed the treatment protocol in the scheduled duration, with 1–2 days interruption of radiation, which was seen in eight patients in conventional fractionation radiotherapy (CFRT) and 13 patients in hypofractionated radiation therapy (HFRT) due to toxicities [Table 2].

**Table 1: Radiation treatment**

| Variables | CFRT | HFRT |
|---|---|---|
| Number of patients | 40 | 40 |
| Total dose | 5000 CGY | 4272 CGY |
| Fractions | 25 | 16 |
| Dose per fraction | 200 CGY | 267 CGY |
| Treatment days per week | 5 days a week | 5 days a week |
| Total treatment period | 5 weeks | 3.1 weeks |

HFRT: Hypofractionated radiation therapy, CFRT: Conventional fractionation radiotherapy

**Table 2: Characteristics of patients**

| Characteristics | CFRT (%) | HFRT (%) |
|---|---|---|
| Age (years) | | |
| 30–40 | 14 (35) | 18 (45) |
| 40–50 | 17 (43) | 12 (30) |
| 50–60 | 9 (23) | 10 (25) |
| ECOG score | | |
| 0 | 4 (10) | 8 (20) |
| 1 | 17 (43) | 20 (50) |
| 2 | 19 (47) | 12 (30) |
| Menopausal status | | |
| Pre | 14 (35) | 22 (55) |
| Post | 18 (45) | 13 (33) |
| Peri | 8 (8) | 5 (12) |
| Hormone therapy | | |
| ER+ | 15 (38) | 16 (40) |
| PR+ | 16 (40) | 12 (30) |

HFRT: Hypofractionated radiation therapy, CFRT: Conventional fractionation radiotherapy

**Table 3: Characteristics of tumor**

| Characteristics | CFRT (%) | HFRT (%) |
|---|---|---|
| Anatomical side | | |
| Left | 20 (50) | 18 (45) |
| Right | 20 (50) | 22 (55) |
| Involved breast quadrant | | |
| Upper outer quadrant | 24 (60) | 23 (58) |
| Other quadrants | 16 (40) | 17 (42) |
| Tumor stage | | |
| II | 22 (55) | 25 (63) |
| III | 18 (45) | 15 (37) |
| Tumor grade | | |
| I | 5 (13) | 2 (5) |
| II | 18 (45) | 24 (60) |
| III | 17 (42) | 14 (35) |

HFRT: Hypofractionated radiation therapy, CFRT: Conventional fractionated radiotherapy

Regarding toxicities, Grade I–II acute skin reactions were observed in 19 patients (48%) of CFRT and 22 patients (55%) of HFRT. Grade III skin toxicities were observed in 6 patients (15%) in CFRT and in 16 patients (40%) of HFRT. Acute radiation-induced pneumonitis was noticed in 2 patients (5%) in CFRT and in 4 patients (10%) of HFRT. The development of dysphagia was equal in both groups, in 9 patients and did not cause much disturbance to the patients in continuation of the treatment, managed with Ryle's tube and other supportive measures. Anemia was noticed in 18 patients (45%) of CFRT and 23 patients (58%) of HFRT. Febrile neutropenia was observed in 4 patients (10%) of CFRT and in 7 patients (18%) of HFRT [Tables 3-5].

Lymphedema is a common late complication resulting from both axillary nodal dissection and radiotherapy. One year of follow-up, 8 patients (20%) in CFRT and 13 patients (33%) in HFRT presented with lymphedema. Restricted arm and shoulder movement were noticed in almost all patients in both groups with varying intensity. Lymphedema and restricted shoulder movement were reduced with regular exercises. Some patients developed transient hypertension after 3 months of completion of treatment. One patient in HFRT with left-sided breast cancer developed minimal pericardial effusion at 6 months of follow-up. At 1 year of follow-up, two patients presented with lung metastasis and one patient with bone metastasis in the CFRT group. In

**Table 4: Acute skin reactions**

| Acute skin reactions | CFRT (%) | HFRT (%) |
|---|---|---|
| Grades I and II | 48 | 55 |
| Grade III | 40 | 15 |

HFRT: Hypofractionated radiation therapy, CFRT: Conventional fractionated radiotherapy

**Table 5: Development of anemia and febrile neutropenia during radiation**

| Complication | CFRT | HFRT |
|---|---|---|
| Anemia (%) | 45 | 58 |
| Neutropenia | 10 | 18 |

HFRT: Hypofractionated radiation therapy, CFRT: Conventional fractionated radiotherapy

**Table 6: Late complications at 1 year of follow-up**

| Toxicity | CFRT (%) | HFRT (%) |
|---|---|---|
| Lymphedema | 8 (20) | 13 (33) |
| Chest wall recurrence | 2 (5) | 1 (3) |
| Axillary nodal recurrence | 1 (3) | 0 (0) |
| Lung metastasis | 2 (5) | 0 (0) |
| Liver metastasis | 0 (0) | 1 (3) |
| Bone metastasis | 1 (3) | 1 (3) |

HFRT: Hypofractionated radiation therapy, CFRT: Conventional fractionated radiotherapy

HFRT group, one patient presented with liver metastasis and one patient with bone metastasis. Regarding chest wall recurrence, one patient presented at 6 months and two patients at 1 year in CFRT. In HFRT, one patient had chest wall recurrence at 1 year of follow-up. Recurrence in axillary nodes was observed in one patient in CFRT, 1 year after completion of treatment [Table 6].

The other possible chronic toxicities are as follows:

1. Skin changes
2. Damage to rib bones
3. Pain and numbness in the arm
4. Hypothyroidism
5. Radiation-induced second cancers such as leukemia, thyroid, and breast.

These changes will occur months to years after treatment. Some of the toxicities and other complications may be related to mastectomy induced the cosmetic appearance of the chest wall, side of the breast cancer and the breast quadrant of the tumor. However, there is no concrete evidence for this association. The statistical analysis of all the characteristics of the patients, results, and toxicities is discussed in the following tables and figures.

## DISCUSSION

Adjuvant local or locoregional radiation treatment improves locoregional control and survival for women treated with breast-conserving surgery and in patients with the high-risk disease treated with mastectomy. Standard or conventional fractionation radiotherapy for breast cancer is generally defined as 1.8–2 Gy per fraction to total doses of 50–50.4 Gy. Early experiences of hypofractionated radiation regimen using higher fraction sizes to deliver radiotherapy over shorter durations were far from positive. Investigators from Manchester and Denmark have reported an unexpected high rate of late effects, including severe fibrosis among women treated with over 12 fractions.[19] The routine use of HFRT in breast radiotherapy is supported by the results of five large randomized controlled trials (RCTs) in women with early breast cancer.[20-23] These studies demonstrate that HFRT yields equivalent or improved outcomes in all essential endpoints: Efficacy, toxicity, cosmesis, and cost-effectiveness. HFRT also results in greater patient convenience and resource efficiency. Nevertheless, the optimal fractionation schedule is not well established, but existing evidence suggests that shorter schedules may be equivalent with regard to local control and cosmesis. In 2010, a Cochrane review concluded that HFRT did not seem to decrease safety and efficacy, but the longer follow-up was needed for a more comprehensive assessment.[24] Recently, some newly original trials reported the research results[23-27] and several key RCTs update the results with longer periods of follow-up.[28] Thus, we performed this systematic review and meta-analysis to determine the efficacy and safety of altered radiation fraction size on outcomes for women with early breast cancer and to further facilitate clinical decision-making. Studies have evaluated correlations between lungs dose-volume histogram metrics (Vx: Volume of lungs receiving at least x dose, mean lungs dose, etc.) and risk of radiation pneumonitis.[29] In the last quantitative analyses of normal tissue effects in the clinic review, it was concluded that recommendations for dose-volume limits for lungs are challenging as there is no clear and consistent threshold for metrics.[30] One of the valid concerns with using hypofractionation for locoregional radiotherapy is that there may be an increased risk of nerve injury; particularly, radiation-induced brachial plexopathy. One older study reported that the risks of radiation-induced brachial plexopathy and paralysis were high and that the risks increased over long-term follow-up.[31]

## CONCLUSION

From this prospective study, it is clearly evident that hypofractionated radiotherapy in post-mastectomy breast cancer patients is not inferior to conventional radiotherapy and can be considered a safe and feasible alternative treatment protocol. Skin toxicities are slightly higher in hypofractionated radiotherapy. All other adverse effects are nearly comparable to conventional radiotherapy. A shorter course of treatment in a broader range of patients may improve patient compliance and decrease resource utilization. Completion of uninterrupted radiation treatment in a shorter duration increases the biological effects of radiation. Most of the studies having a long follow-up of patients after completion of radiation treatment provide strong evidence of non-inferiority of this approach compared with conventional fractionation. We can also argue that acute toxicities should not be a limiting factor for hypofractionated radiotherapy considering other benefits over the conventional regime. The optimal modality for treating breast cancer is still a challenge, despite several studies being conducted in many centers worldwide. In particular, the best adjuvant radiation protocol after post-mastectomy breast cancer patients is still an open issue in the era of customization of cancer therapy. Considering all aspects of adjuvant radiotherapy, we can conclude that this trial will substantially contribute to the understanding of the hypofractionated regimen is not only aiming at obtaining an optimal disease control but also preserving the patient quality of life and this kind

of adjuvant treatment is highly suitable for patients in developing countries like India.

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