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Original Research

# Feasibility and Toxicity Profile of Hypofractionated Post- Mastectomy Radiation Therapy in Breast Cancer Patients

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**Introduction:** Post-mastectomy radiation therapy (PMRT) is a crucial part of breast cancer treatment. Hypofractionated radiation therapy, although more commonly used after breast conservation surgery, has emerged as a newer modality. However, there is a limited understanding of its feasibility and toxicity profile specifically in PMRT. This study aimed to describe the clinical outcomes and toxicity profile of breast cancer patients undergoing hypofractionated 3D conformal radiation therapy for PMRT.

**Materials and Methods:** This retrospective study included breast cancer patients aged 18 and above who were eligible for adjuvant PMRT between April 2021 and October 2022. The treatment regimen consisted of 40.05Gy delivered in 15 fractions over 3 weeks using 3D conformal radiation therapy. Dosimetric parameters for target volumes and organs at risk were analyzed, and toxicities such as hematologic, dermatitis, and pharyngitis were monitored.

**Results:** A total of 71 patients were included in the study, with 70 females and 1 male. The majority of patients (46%) belonged to the 46-55 years age group, with an age range of 34 to 85 years and a mean age of 52 years. Clinical Stage IIIA was the most common stage (29.5%), followed by Stage IIB (25.3%). The majority of patients received adjuvant chemotherapy (52%). The mean treatment time was 21 days, and all patients completed treatment without any major complications. The follow-up period ranged from 17 to 27 months. One patient expired due to a non- cancer-related cause, and four patients experienced disease progression or distant metastasis. Dosimetric analysis revealed satisfactory coverage of the planned target volume, with heart V17Gy ranging from 1.27% to 12.5% and heart V35Gy ranging from 0.16% to 7.2%. The most common adverse effect observed was dermatitis, followed by fatigue, throat pain, and shoulder pain. Blood parameters remained stable throughout the treatment course.

**Conclusion:** Hypofractionated PMRT was well tolerated in the study group, with no major acute reactions or treatment interruptions observed. Our findings support the feasibility and safety of this treatment approach in breast cancer patients. Special attention should be given to respiratory motion management, particularly in left-sided disease, to achieve optimal dose constraints.

## Introduction

Breast cancer is one of the leading causes of death in both developing and developed countries. Improving life expectancies has lead to increasing incidences in cancer [1]. Incidence rates are increasing irrespective of urban and rural status [2]. In India, majority of patients present with locally advanced stages. Treatment involves neoadjuvant chemotherapy, modified radical

mastectomy and post mastectomy radiation therapy. Treatment of breast cancer continues to keep evolving over time.

Radiation therapy evolved to have a major role in treatment of breast cancer. In 2005, EBCTCG meta-analysis, radiation therapy to the chest wall and regional lymphatics reduced 5-year LRR by 17% [3]. EBCTCG also showed radiation therapy after breast conservation surgery conferred similar results [4]. Breast cancer management needs multidisciplinary care. Major management of breast cancer often spans over 3 months to 9 months. Radiation therapy usually contributes to about 5-6 weeks. So time factor plays a important concern. The need of radiation therapy in breast cancer is increasing all over the world & studying the biology of breast cancers also has lead to usage of small fractions with higher doses throughout the world.

Concept of hypofractionation initially tried in the United Kingdom as early as 1986. Case series and cohort studies initially reported that these shorter schedules were acceptable in terms of both acute reactions and local control. So reducing the fraction from five weekly to three weekly schedules have proved to be feasible in terms of tumor control & toxicity. Since then several randomized studies have been conducted on this shorter fractionation regimens, the landmark trials being the START A and START B trials [5-7]. Hypofractionation studies on early breast cancer showed similar local tumor recurrence and late toxicity similar to conventional fractionation.

Concept of hypofractionation became the standard of care in patients with breast conservation surgery. Hypofractionation after mastectomy is slowly gaining support in India. But many studies are based on breast conservation patients & data towards post mastectomy radiation are fewer comparatively. In countries like India, hypofractionation is very helpful in reducing hospital stay thereby reducing infection rates, also particularly for economically less privileged patients & indirectly reduces cost of treatment. Indian breast cancer scenario will definitely benefit from this well established treatment regimen.

Aim of the study is to describe the clinical and toxicity profile of patients undergoing hypofractionated 3D conformal radiation therapy in breast cancer patients.

# Materials and Methods

After getting approval from Institution scientific and ethics committee, patients were accrued for the study. All post mastectomy patients who presented to department of radiation oncology were screened for the study based on inclusion and exclusion criteria. Period of study is from April 2021 to October 2022, period of 18 months. Inclusion Criteria is any patient requiring post mastectomy radiation therapy, who are above 18 years were eligible. Exclusion criteria are age less than 18 years, patients planned for whole breast radiation therapy, Collagen vascular disease, Poor performance status (ECOG>3), Pregnancy & breastfeeding, Breast reconstructed patients, Axillary nodal involvement with extra nodal extension, Metastatic breast cancer, Prior history of radiation to chest, Myocardial infarction within 6 months, chronic heart condition, chronic lung condition, active lung infection, Patient preference for conventional fractionation.

## 3DCRT Procedure

All patients requiring post mastectomy radiation therapy were screened for the study based on inclusion and exclusion criteria after explaining the study and getting informed consent. Radiation therapy was started after healing of surgical wound or four weeks after chemotherapy. Metastatic workup is done for all patients. Echocardiogram was obtained before starting radiation therapy for left sided breast cancer patients.

## CT Simulation

Patient immobilization was done using a breast board. Patient was positioned in supine position with arm abducted 90 degrees or greater. 5 mm cuts were used. Contrast was not used.

## Contouring and Planning

Regions treated were chestwall and supraclavicular field in all patients. RTOG contouring guidelines were used to contour organs at risk, chest wall and supraclavicular field. Planned target volume (PTV) of 5mm is given for supraclavicular region. Bolus was not used for any patients.

## Organs at Risk (OAR)

Lungs, Heart, Liver, Spinalcord, Contralateral breast, and Esophagus were contoured.

## Dose Prescription

40.05 Gy in 15 fractions over 3 weeks.

## Treatment Execution

After contouring and dose prescription, 3DCRT planning was done. Tangential beams were used for chestwall. Anterior beams were used for supraclavicular field. Planning was done in Eclipse planning software, Varian systems. 6 MV beams were commonly used. Plan evaluation was done using Dose Volume Histograms (DVH) and isodose distributions. Final plan was selected based on above parameters. Daily imaging (kV) was done for 3 days for treatment verification, followed by weekly imaging. CBCT was used whenever necessary.

## Weekly Assessment and Followup

During treatment, patients regularly monitored. Patients symptoms if any were recorded. Weekly assessments were done. If any acute reactions were present, grading was done based on RTOG criteria .Patient followed up every 4-6 weeks. Radiation reactions were monitored for response. Disease progression if present were recorded.

## Statistical Analysis

Baseline data like demographics, disease characteristics, comorbidities of the patient are recorded in data entry sheet. Radiation therapy details like DVH parameters, date of starting and completion of radiation therapy are also recorded. Data was analyzed using SPSS 20.0 software. Data was represented graphically using appropriate diagrams. Frequencies and percentages were calculated for discrete variables like hormone status, grade, comorbidities etc. Mean, median and standard deviation were calculated for continuous variables like age. Correlation between variables were studied.

# Results

## Patient Characteristics

Of 71 patients, 70 patients were female and 1 is male. Majority (46%) of patients belonged to 46-55 years age group. Age ranged from 34 to 85 years. Mean age is 52 years. 51% patients were ECOG performance status 1.

The study group had 49% patients with comorbidities, diabetes mellitus (54%) being the most common followed by hypertension (27%), hypothyroidism (14%). 4 patients had previous history of hysterectomy and 5 patients had family history of breast cancer (3 patients had second degree relative with cancer and 2 patients had first degree relative with cancer). Most patients have 2 children and mean breast feeding time of 10 months (Table 1).

| S. No | Variable | Number |
|---|---|---|
| 1 | Sex | Female – 70 |
| | | Male – 1 |
| 2 | Age | < 35 years – 2 |
| | | 36-45 years – 12 |
| | | 46-55 years – 33 |
| | | 56-65 years – 17 |
| | | > 65 years - 7 |
| 3 | Comorbidities (n = 35) | Type 2 Diabetes mellitus - 19 |
| | | Systemic hypertension - 10 |
| | | Hypothyroidism - 5 |
| | | Heart disease - 1 |
| 4 | Laterality | Right sided – 37 |
| | | Left sided - 34 |
| 5 | Clinical stage at presentation | I – 1 |
| | | IIA – 12 |
| | | IIB – 18 |
| | | IIIA – 21 |
| | | IIIB – 15 |
| | | IIIC - 4 |
| 6 | Chemotherapy | Upfront Neoadjuvant chemotherapy – 12 |
| | | Adjuvant chemotherapy – 37 |
| | | Neoadjuvant and adjuvant chemotherapy - 22 |
| 7 | Receptor status | Luminal A – 22 |
| | | Luminal B – 23 |
| | | Her 2 enriched – 8 |
| | | Triple negative - 18 |
| 8 | Pathological stage | I – 1 |
| | | IIA – 14 |
| | | IIB – 20 |
| | | IIIA – 20 |
| | | IIIB – 7 |
| | | IIIC - 3 |

**Table 1. Characteristics of Patients.**

37 patients had right sided disease and 34 patients had left sided disease. Upper outer quadrant (46.4%, n=33) was the most involved site followed by central quadrant. Clinical Stage IIIA was the

most common stage with 29.5% patients followed by Stage IIB with 25.3% patients. 97% patients have invasive ductal cancer- NOS type. Pathological stage IIIA (28.1%) and IIB (28.1%) were most common. Complete response was seen in 6 patients. 12 patients received upfront neoadjuvant chemotherapy, 37 % patients received adjuvant chemotherapy alone and 22 patients received both neoadjuvant and adjuvant chemotherapy. Adriamycin and Cyclophosphamide followed by Paclitaxel was the most common regimen followed in both neoadjuvant and adjuvant chemotherapy settings.

Mean treatment time is 21 days. Treatment time ranged from 19 to 26 days. All patients completed treatment without any major complications. Follow up ranged from 17 months to 27 months. Out of 71 patients, 1 patient expired on follow up after 4 months of radiation therapy. She expired due to non cancer related cause (Chronic pancreatitis). On followup, 3 patients had distant metastasis alone (lung metastasis, bone metastasis,brain metastases) and 1 patient had both local disease and distant metastasis. 3 patients who progressed had stage IIIC disease & 1 had stage IIIB disease. These patients are on systemic therapy and doing well. All other patients are disease free at the time of last follow up.

## Acute Toxicities

### Dermatitis

Dermatitis was the most common adverse effect in this study. None of the patients had grade III or IV dermatitis (Table 2).

| Dermatitis | Week 1 | Week 2 | Week 3 | Week 6 |
|---|---|---|---|---|
| | (During RT) | (During RT) | (During RT) | (Post RT) |
| | n patients | n patients | n patients | n patients |
| Grade I | 0 | 34 | 60 | 39 |
| Grade II | 0 | 0 | 7 | 32 |
| Grade III | 0 | 0 | 0 | 0 |
| Grade IV | 0 | 0 | 0 | 0 |

**Table 2. Dermatitis Pattern in treated Patients.**

### Fatigue

31 patients (43.6%) developed fatigue during treatment. They continued their daily activities without any limitations.

### Cough

Dry cough was observed in 18 patients (25.3%) during 3$^{rd}$ week of radiation therapy. No radiographic changes were observed.

### Throat pain (Pharyngitis)

Throat pain was the next common adverse effect. 35 patients (49.2%) had throat pain, of which 2 patients had it in 1$^{st}$ week, 21 patients had it in 2$^{nd}$ week and 12 patients had it in 3$^{rd}$ week. They were treated with non opioid analgesics. None of the patients had complaints of pharyngitis at the time of follow-ups (Table 3).

| Pharyngitis | Week 1 | Week 2 | Week 3 | Week 6 |
|---|---|---|---|---|
| | (During RT) | (During RT) | (During RT) | (Post RT) |

| | n patients | n patients | n patients | n patients |
|---|---|---|---|---|
| Grade I | 2 | 21 | 12 | 0 |
| Grade II | 0 | 0 | 0 | 0 |
| Grade III | 0 | 0 | 0 | 0 |
| Grade IV | 0 | 0 | 0 | 0 |

**Table 3. Pharyngitis Pattern.**

### Shoulder Pain

Shoulder pain was observed in 10 patients (14%) during treatment. All these patients had previous history of shoulder pain which developed after surgery. These patients had physiotherapy and their symptoms was relieved.

### Blood Parameters

Blood parameters were monitored weekly during treatment. No changes were observed.

## DVH Parameters (Table 4)

| Parameter | Range | |
|---|---|---|
| | Right sided | Left sided |
| V90% | 90.4% to 99% | 90.3% to 96.5% |
| V95% | 86% to 95.1% | 84% to 93% |
| Global max | 105% to 110% | 107.3% to 110% |
| V105% | 0.5% to 4.78% | 1.8% to 5.3% |
| V107% | 0% to 0.5% | 0% to 0.6% |

**Table 4. Target Coverage.**

### OARS

Contralateral breast - All patients were within dose tolerance limits. Mean dose to contralateral breast is 104 cGy. Spinal cord tolerances were within normal limits (Table 5, 6 and 7).

| Parameter V17Gy | Range | |
|---|---|---|
| | Right sided | Left sided |
| Ipsilateral lung | 16.97% to 28.7% | 12.64% to 22.92% |

**Table 5. Lung Dose.**

| Parameter | Range | |
|---|---|---|
| Heart | Right | Left |
| Mean dose | 35.3 cGy to 152.6 cGy | 135.7 cGy to 712 cGy |

**Table 6. Heart Mean Dose.**

| Parameter | Range |
|---|---|
| V17Gy | 1.27% to 12.5% |
| V35Gy | 0.16% to 7.2% |

**Table 7. Heart Parameters.**

# Discussion

Hypofractionated radiotherapy is an established regimen for treating breast cancers. But most studies are based on whole breast radiation therapy. Post mastectomy hypofractionated radiation therapy trials are fewer compared to whole breast radiation. In the landmark START trials, only 8% had post mastectomy radiation therapy [5-7].

Skin toxicity was minimal and well tolerated as seen as in other studies [8]. Dermatitis started from second week of radiation therapy. Majority of patients experienced dermatitis during third week. Odynophagia (Pharyngitis) was seen from second week of radiation therapy and required step 1 analgesics. It was well tolerated. None of them had grade 3 pharyngitis or required break in treatment.

This study was conducted during covid pandemic. Hypofractionation needed less hospital stay and hence less chance of transmission. Hypofractionation also reduced machine's workload. So more patients can be treated during similar time. This is particularly advantageous in developing countries like India. Cosmetic effects need to be studied for longer time.

Most women in our study were in the age group of 46 to 55 years (46.4%, n=33). Most of these women are working women and some are even sole earners for their family. So, conventional fractionation of 23 to 25 fractions leads to more work hours lost and thereby earnings for their family. Also costs during stay of treatment in hospital can lead to increased spending like food costs, room costs for their relatives etc.

Nearly 34 patients had children less than 15 years old and so care for them during treatment is difficult for the patient. Costs for travel and difficulty to travel during covid crisis complicated the treatment. So, hypofractionated treatment completing within 3 weeks is an advantageous treatment. In a study by Bekelman et al [9], hypofractionation permitted savings of 10% for health care expenditures. Yang et al showed significant reduction in cost in multiple countries [10]. Indian scenario also shows similar findings. Hypofractionation also permits savings for patient.

### *Limitations*

This study is based on a single institution and was not a randomised study. Multi institutional randomized controlled trials are necessary to evaluate hypofractionation in Indian context. Respiratory motion management was not utilized in many patients, only 4 patients had motion management. Dose to Cardiac substructures like Left Anterior Descending Artery (LAD) were not studied. Patients were followed up for short duration (Mean follow up period was 22 months), so late effects of treatment were not known. Economic benefits of hypofractionation and Quality of Life assessment were not studied.

In conclusion, Hypofractionated post mastectomy radiation therapy is well tolerated in our study group. Patients completed their treatment without any breaks during treatment. Respiratory motion management especially left sided disease patients should be used for achieving dose constraints.

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