**Conventional Versus Different Hypofractionated Radiotherapy Dosage Schedules in Postmastectomy Advanced Breast Cancer**

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**Abstract**

**Introduction:** The standard treatment for advanced breast cancer is surgery consisting of breast-conserving surgery or modified radical mastectomy (MRM) postneoadjuvant chemotherapy followed by adjuvant radiation treatment (RT). Conventionally-fractionated whole breast irradiation has been the standard RT regimen, but recently shorter courses of hypofractionated whole breast or chest wall irradiation have been advocated for patient convenience and reduction in healthcare costs and resources. Radiation is delivered through the same technique, but tumors receive a higher dose of radiation per treatment session with hypofractionation. **Aim:** The aim of the study was to compare different fractionation schedules of radiotherapy in postoperative cancer breast with respect to locoregional control and toxicities. **Materials and Methods:** One hundred and eighty-eight patients of cancer breast, who received RT between January 2017 and December 2019 were assessed. Since hypofractionation is well documented and established and being practiced in prestigious institutes, we treated the patients as per their choice to receive 10.15 or 25 fractions. 72 patients (Group A) were treated with conventional fractionation to a dose of 50 Gy/25 fractions/5 weeks. Second group of 62 patients (Group B) were given 40.5 Gy/15 fractions/3 weeks and third group of 54 patients (Group C) were treated with 34 Gy/10 fractions/2 weeks. All patients were T3 or more and underwent MRM after neoadjuvant chemotherapy. They were in the age group of 30–65 years. All of them received adjuvant chemotherapy and hormone therapy in case of estrogen/and progesterone receptor positivity and anti-Her2neu target therapy in case of Her2neu positivity. They were assessed for locoregional control and acute and chronic toxicities. **Results:** Grade 3 and 4 skin toxicity was similar in all three groups. At 6 months postcompletion of RT, two patients in Group A, 3 in Group B, and 5 in Group C lost to follow-up. In rest of the subjects, there was no locoregional failure. At 1 year, 1 patient from Group A, 2 from Group B, and 1 from Group C developed locoregional recurrence. There were no major chronic toxicities. Arm edema and Telangiectasia were similar in three groups. No rib fracture or major cardiotoxicity and pulmonary toxicity was seen. **Conclusion:** Hypofractionated RT is a part of the typical treatment regimen for breast cancer nowadays. The major advantage is of convenience to the patients as it is completed the full course of RT in fewer sessions. With both conventional and hypofractionated radiation, the patient receives radiation 5 days a week. In the conventional regimen, though the schedule lasts for 5 weeks, whereas hypofractionation therapy is completed in 2 to 3 weeks. Local control wise both conventional and hypofractionated regimen is similar in locoregional control and toxicity. Therefore, hypofractionated RT should be practiced in cancer breast as it is economical, convenient, and toxicity wise and result wise similar to conventional radiotherapy.

**Keywords:** Breast, hypofractionation, radiotherapy

**INTRODUCTION**

The standard treatment for advanced breast cancer is surgery consisting of breast-conserving surgery or modified radical mastectomy (MRM) postneoadjuvant chemotherapy followed by adjuvant radiation treatment (RT). Conventionally-fractionated whole breast irradiation (CF-WBI) has been the standard RT regimen, but recently shorter courses of hypofractionated whole breast or chest wall irradiation have been advocated for patient convenience and reduction in healthcare costs and resources. Like conventional radiation therapy, the aim of hypofractionation is to destroy cancer cells in the breast,
but with larger radiation doses in fewer overall sessions. Conventional radiation typically requires 25–30 sessions whereas hypofractionation requires 10–15. Hypofractionation is a form of external beam radiation therapy that emits high-energy X-ray beams carefully aimed at the breast. Radiation is delivered through the same technique, but tumor receives a higher dose of radiation per treatment session with hypofractionation. Hypofractionated schedules are potentially attractive in the treatment of breast carcinoma. From radiobiological point of view, the linear quadratic model suggests that when the α/β ratio of the tumor is the same or less than that of the critical normal tissue, a larger dose per fraction (hypofractionation) with a modest decrease in total dose is equally or potentially more effective than conventional fractionation. An estimate of 4 Gy for α/β value has been already reported for the fractionation sensitivity of breast cancer. The low estimated α/β ratio for breast cancer means that it is probably as sensitive to fraction size as is dose-limiting normal tissue, and hypofractionation for breast cancers is actually advantageous. Thus, breast cancer is a promising field for hypofractionated schedules of irradiation. In most of the centers, fluoroscopic simulation and two-dimensional planning techniques with physical wedges are used. With modern planning techniques, including computed tomography (CT)-based three-dimensional planning, prone positioning, and deep-inspiration breath hold (DIBH) or respiratory gating, the incidence of radiation-related late toxicities has further minimized whether using hypofractionated-whole breast irradiation (HF-WBI) or CF-WBI. Early practice of hypofractionated postmastectomy radiotherapy (PMRT) in the 1960s and 1970s resulted in critical side effects like shoulder dysfunction, arm edema, lung fibrosis, brachial plexopathy, and arm paralysis.[1-3] In these studies radiation dose per fraction was increased without appropriately modifying total dose and used conventional archaic beam planning that caused hot spots in the supraclavicular area, resulting in extremely high radiobiological doses to normal tissues including the brachial plexus. Radiobiology concepts are better studied now and planning techniques and systems have become much more sensitive and sophisticated. An additional issue that needs to be resolved in the postmastectomy setting is whether complications during breast reconstruction are exacerbated by hypofractionation, which is already seen with CF PMRT.[4,5]

### Aim

The aim of the study was to compare different fractionation schedules of radiotherapy in postoperative cancer breast with respect to locoregional control and toxicities.

### Materials and Methods

One hundred and eighty eight patients of cancer breast, who received RT between January 2017 and December 2019 were assessed. They were in age group of 30–65 years [Table 1]. All of them received adjuvant chemotherapy and hormone therapy in case of Estrogen/and Progesterone receptor positivity and anti-Her2neu target therapy in case of Her2 neu positivity. Since hypofractionation is well documented and established and being practiced in prestigious institutes we treated the patients as per their choice to receive 10.15 or 25 fractions. Seventy-two patients (Group A) were treated with conventional fractionation to a dose of 50 Gy/25 fractions/5 weeks. Second group of 62 patients (Group B) were given 40.5 Gy/15 fractions/3 weeks and third group of 54 patients (Group C) were treated with 34 Gy/10 fractions/2 weeks. All patients were node positive, locally advanced T3 or more and underwent MRM after neoadjuvant chemotherapy. Patients were immobilized and simulated and CT planning was done to receive Intensity Modulated Radiation Therapy. 6 MV photon were used and cone beam computed tomography imaging sessions were done weekly. Dose to lungs, heart, spinal cord, and brachial plexus was kept within tolerable limits [Table 2]. Treatment area included chest wall, ipsilateral axilla, and ipsilateral supraclavicular nodal area. MRM scar was given Simultaneous Integrated Boost (SIB) with wax bolus. Biological effective dose was 75, 66.78, 62.90 for 50 Gy, 40.05 Gy, and 34 Gy, respectively (alpha/ beta = 4). Patients were assessed for locoregional control, acute and chronic toxicities after completion of radiotherapy, at 6 months and 1 year posttreatment.

### Results

At 6 months postcompletion of RT, two patients in Group A, 3 in Group B, and 5 in Group C lost to follow-up. In rest of the subjects, there was no locoregional failure. At 1 year, 2 patients from Group A, 2 from Group B, and 1 from Group C developed locoregional recurrence [Table 3]. After completion of treatment and up to 1 month postradiation, skin toxicity was similar in all three groups. The grading was done as per radiation therapy oncology group scale.

### Table 1: Patient characteristics

| Poll | Group A (%) | Group B (%) | Group C (%) |
|------|-------------|-------------|-------------|
| Premenopausal | 30/72 (41.66) | 22/62 (35.48) | 19/54 (35.18) |
| Postmenopausal | 42/72 (58.34) | 40/62 (64.52) | 35/54 (64.82) |
| T3 | 50/72 (69.44) | 41/62 (66.12) | 24/54 (44.44) |
| T4 | 22/72 (30.56) | 21/62 (33.88) | 40/54 (55.56) |

### Table 2: Organ at risk doses

| Organ at risk | Group A (Gy) | Group B (Gy) | Group C (Gy) |
|--------------|--------------|--------------|--------------|
| Heart (mean) | 11.6-13.6 | 6.8-9.2 | 6.2-8.4 |
| Heart (V30) | 1.6-1.9 | 0.8-1.7 | 0-0.5 |
| Lung ipsilateral (V20) | 17.1-19.33 | 10.6-12.2 | 6.8-8.4 |
| Lung ipsilateral (V5) | 44.2-47.1 | 32.1-34.4 | 27.2-29.8 |
| Lung contralateral (V20) | Nil | Nil | Nil |
| Lung contralateral (V5) | 28.1-32.6 | 13.6-15.3 | 11.9-13.1 |
| Spinal cord (maximum) | 18.4-22.5 | 14.1-16.3 | 14.4-16.6 |
| Brachial plexus (maximum) | 36.2-41.8 | 26.9-30.2 | 14.8-26.4 |
There were no major chronic toxicities. Arm edema and telangiectasia were similar in three groups. No rib fracture, brachial plexopathy, or major cardiotoxicity was seen.

**Discussion**

Practice of PMRT has increased in the last decade, and most patients who undergo PMRT require regional nodal irradiation (RNI) that includes radiation to the axillary, supraclavicular, and/or internal mammary nodes, therefore vital structures and organs like brachial plexus, heart, and lungs at risk of postradiation toxicity. Although the standard of care for locally advanced breast cancer is breast conservation after downstaging with neoadjuvant chemotherapy, many women with locally advanced breast cancer still are not fit for breast conservation and undergo mastectomy. PMRT in the past was limited to patients with four or more positive nodes, but recent studies have shown improved locoregional control and survival in postmastectomy patients with any number of positive nodes.

The vast majority of patients enrolled in the major randomized trials had early-stage T1-2 N0 tumors and underwent breast-conserving surgery, with only a minority of all patients receiving RNI (11%). Long-term follow-up of the Start trials did not show any increased rates of shoulder stiffness or arm edema in those receiving RNI with HF-WBI versus CF-WBI. In this study, there was only one case of brachial plexopathy out of >4400 patients, which clearly show that modern techniques for hypofractionated RNI are much safer than in past. In the clinically relevant 40 Gy arm of the Start B trial, breast shrinkage, telangiectasias, and edema instead showed improvement at 10 years compared to CF-WBI, while other late toxicities showed no difference. Long-term analysis of the Start A and B trials have additionally shown very low rates of cardiac toxicities (0.8% and 1.1%, respectively), symptomatic rib fractures (0.1% and 0.3%), and postradiation pneumonitis (0.1% and 0.5%), with no differences between HF-WBI and CF-WBI arms. There were 26 and 17 cardiac deaths in the Start A and B trials, respectively, with no significant difference between HF-WBI and CF-WBI. No differences in late skin or subcutaneous tissue toxicity were seen in the OCOG trial. Similarly, long-term update of the OCOG trial reported 21 total cardiac deaths with no significant differences between arms.

In a single-arm, prospective phase II study Khan et al. tested hypofractionated PMRT including RNI (36.63 Gy in 11 fractions with an optional scar boost of 12.32 Gy in 4 fractions) in 69 patients with Stage II-IIIC breast cancer. Three-year local-and-distant-recurrence free survival were similar 89.2% (95% confidence interval [CI]: 0.749–0.956) versus 90.3% (95% CI: 0.797–0.956), respectively. There were no grade three acute or chronic toxicities. Another Phase II trial studied hypofractionated RNI delivered in the prone position after breast-conserving surgery or mastectomy in 69 patients with Stage IB-IIIA breast cancer. The dose regimen consisted of 40.5 Gy in 15 fractions with a simultaneous integrated boost of 0.5 Gy for a total of 48 Gy to the tumor bed. Three-year breast cancer-specific survival was 95.6% with no locoregional recurrences after a median follow-up of 35 months. This trial also demonstrated favorable late toxicities, with only one grade 2 lymphedema, and no case of brachial plexopathy. Investigators from the Chinese Academy of Medical Sciences completed a randomized trial comparing hypofractionated PMRT (43.5 Gy in 15 fractions) to CF PMRT (50 Gy in 25 fractions) with RNI and no scar boost. From 2008 to 2016, patients with primarily stage III disease were enrolled and randomized. Initial results were presented at the 2017 ASTRO annual meeting. There were no significant differences in 5-year locoregional recurrence (8.4% vs. 6.0%; P = 0.396), disease-free survival (75.1% vs. 74.6%; P = 0.841), or overall survival (84.9% vs. 87.1%; P = 0.562). The incidence of radiation pneumonitis, lymphedema, shoulder dysfunction, and ischemic heart disease was similar between groups, while incidence of grade three acute skin toxicity was lower in the hypofractionated than conventional group. There were no cases of brachial plexopathy. Only drawback of this trial was that breast reconstruction was not allowed. Most of the patients undergoing mastectomy opt for breast reconstruction, with an increasing trend making it difficult to extrapolate these results to the reconstructed population.

None of the major trials reported on acute toxicity; however, in the MDACC trial, overall acute grade two and three effects were significantly reduced with HF-WBI as compared to CF-WBI, and several patient-reported better functional outcomes at 6 months. In another prospective observational study of 2309 patients, patients who received HF-WBI had lower physician-assessed moist desquamation (6.6% vs. 28.5%, P < 0.001) and any grade two or higher dermatitis (27.4% vs. 62.6%, P<0.001) compared to those who received CF-WBI.

A prospective trial examined the use of prone versus supine position and found that prone positioning was associated with decreased volume of irradiated lung in all patients and irradiated heart in 85% of patients with left-sided breast cancer. However, additional studies have found that DIBH in the supine position may offer better cardiac sparing than the free-breathing prone position. The randomized UK Heart Spare study demonstrated that HF-WBI delivered in the supine position with DIBH resulted in lower mean heart and left anterior descending coronary artery doses than in the prone position. With any of these newer techniques, it is clear that normal structures are receiving far less radiation dose than in the past generation of trials. A study by Darby and colleagues

| Table 3: Locoregional control |
|-----------------------------|
| **Group A (%)** | **Group B (%)** | **Group C (%)** |
| At completion | 72/72 (100) | 62/62 (100) | 54/54 (100) |
| At 6 months | 70/70 (100) | 59/59 (100) | 49/49 (100) |
| At 12 months | 68/70 (97.14) | 57/59 (96.61) | 48/49 (97.95) |
in 2013 reported a 7.4% increase in major coronary events per Gy increase in mean heart dose,\(^{[21]}\) however the average mean heart dose of all 1144 patients with left-sided cancers included in this study was 6.6 Gy – more than five times the average mean heart dose of 1.2 Gy reported for patients on the DBCG trial who were treated with HF-WBI and respiratory gating.\(^{[22]}\) Murray Brunt et al. in a publication in 2020 concluded that 26 Gy in five fractions over 1 week is noninferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumor control, and is as safe in terms of normal tissue effects up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.\(^{[23]}\) In our study the locoregional control was excellent in all three groups. Toxicity was acute skin toxicities of RTOG grade 2, 3 were seen and were manageable. No major chronic toxicity was seen. Dose to heart lungs and spinal cord was kept within tolerable limits.

**Conclusion**

Hypofractionated RT is a part of the typical treatment regimen for breast cancer now a days. The major advantage is of convenience to the patients as it is completes the full course of RT in fewer sessions. With both conventional and hypofractionated radiation, the patient receives radiation 5 days a week. In the conventional regimen, though the schedule lasts for 5 weeks, hypofractionation therapy is completed in 2 to 3 weeks. Both conventional and hypofractionated regimens are similar in locoregional control and toxicity. Therefore, hypofractionated RT should be practiced in cancer breast as it is economical, convenient, and toxicity and result wise similar to conventional radiotherapy.

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**Conflicts of interest**

There are no conflicts of interest.

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