# COMPARISON OF HYPOFRACTIONATED RADIATION THERAPY VERSUS CONVENTIONAL RADIATION THERAPY IN POST MASTECTOMY BREAST CANCER

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**ABSTRACT**

**INTRODUCTION**

Breast cancer is the most common cancer in women worldwide and a leading cause of cancer death in females and accounts for 1.8 million new cases and approximately 0.5 million deaths annually. Patients who present with locally advanced breast cancer (LABC) require multidisciplinary team approach that incorporates diagnostic imaging, surgery, chemotherapy and histopathological assessment, including molecular-based studies, radiation, and, if indicated, biologic and hormonal therapies. Hypofractionated radiation therapy following mastectomy has been used in many institutions for several decades and have demonstrated equivalent local control, cosmetic and normal tissues between 50 Gy in 25 fractions and various hypofractionated radiotherapy prescriptions employing 13-16 fractions. Evidence suggests that hypofractionated radiotherapy may also be safe and effective for regional nodal disease.

**AIMS AND OBJECTIVES**

To compare the local control and side effects of hypofractionated radiation therapy with conventional radiation therapy in post mastectomy carcinoma breast with stage II and III and to compare the tolerability and compliance of both schedules.

**MATERIALS AND METHODS**

The study was conducted on 60 histopathologically proven patients of carcinoma of breast, treated surgically with modified radical mastectomy. Group I patients were given external radiation to chest flap and drainage areas, a dose of 39 Gy/13 fractions/3.1 weeks, a daily dose 3 Gy for 13 fractions in 4 days a week schedule and Group II patients were given external radiation to chest flap and drainage areas, a dose of 50 Gy/25 fractions/5 weeks, to receive a daily dose 2 Gy for 25 fractions in a 5 days a week schedule.

**RESULTS**

The median age at presentation in Group I and II was 48 and 50 years respectively. Locoregional control after completion of radiotherapy in Group I vs. Group II was 26/30 (86.7%) vs. 27/30 (90%) respectively. Acute reactions and their grades in Group I and II were: Skin reactions, grade I-(21/30) 70% vs. (22/30) 73.3%, grade II-(7/30) 23.4% vs. (7/30) 23.4%, grade III-(1/30) 3.3% vs. (1/30)3.3%, grade IV-(1/30) 3.3% vs. nil; oesophageal reactions; grade I-(7/30) 23.3% vs. (12/30) 40%, grade II-(3/30) 10% vs. nil. All the late radiation reactions in Group I were higher than in Group II.

**CONCLUSION**

In this present study, almost similar results were seen in both the groups in terms of local control and side effects. However, hypofractionated schedules have shown same response in terms of tumour control and late normal tissue effects with the advantage of decreased workload, increased compliance and reduced cost of treatment, and can be considered as a reliable alternative in radiation treatment for post mastectomy breast cancer patients.

**KEYWORDS**

Breast Cancer; HFRT; Hypofractionated Radiotherapy; CFRT; Conventional Fractionation; MRM; Modified Radical Mastectomy; LABC.

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**INTRODUCTION:** Breast cancer is the most common cancer in women worldwide and a leading cause of cancer death in females. Worldwide breast cancer accounts for 1.8 million new cases and approximately 0.5 million deaths annually. In India, breast cancer accounts for 0.15 million new cases, which is 14% of all newly diagnosed cancers and 13% deaths of all cancer deaths. Hypofractionated breast radiation therapy following mastectomy has been used in

many institutions for several decades and have demonstrated equivalent local control, cosmetic and normal tissue outcomes with 50 Gy in 25 fractions and various hypofractionated radiotherapy prescriptions employing 13-16 fractions. Evidence suggests that hypofractionated radiotherapy may also be safe and effective for regional nodal disease. In the view of equivalent outcomes, patient convenience and health care utilisation benefits, hypofractionated radiotherapy can be the new standard following modified radical mastectomy.

**AIMS AND OBJECTIVES:** To compare the local control and side effects of hypofractionated radiation therapy with conventional radiation therapy in post mastectomy carcinoma breast with stage II and III and to compare the tolerability and compliance of two schedules.

**MATERIALS AND METHODS:** The study was conducted on sixty histopathologically proven patients of carcinoma breast, treated surgically with modified radical mastectomy and referred for radiation therapy, who attended the Department of Radiotherapy, Regional Cancer Centre, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. These patients were planned to receive post-operative radiation therapy to chest wall and drainage areas.

The pretreatment evaluation in all patients included complete history, general physical examination and complete systemic examination. The assessment of patient's general condition was done using Karnofsky Performance Status (KPS). Haematological assessment was done by complete haemogram and biochemistry profile. Radiological assessment including chest x-ray and ultrasound of abdomen and pelvis was done in all patients. The patients were staged according to (American Joint Committee on Cancer) AJCC 2010 staging system. Excluded were those patients, who had primary tumour less than 5 cm in size, no lymphatic/vascular invasion with free resection margins, who had received surgical treatment other than modified radical mastectomy with prior radiation therapy elsewhere before being entered into the study and those patients who had distant metastasis at presentation.

**METHODOLOGY:** The study was designed as a randomised prospective trial and was conducted on 60 patients divided into 2 groups of 30 patients each by computer generated tables.

**Group I:** This group consisted of randomly selected 30 patients of carcinoma breast who had undergone modified radical mastectomy as surgical treatment. These patients were given external radiation to chest flap and drainage areas, a dose of 39 Gy/13 fractions/3.1 weeks, a daily dose 3 Gy for 13 fractions in 4 days a week schedule.

**Group II:** This group consisted of randomly selected 30 patients of carcinoma breast who had undergone modified radical mastectomy as surgical treatment. These patients were given external radiation to chest flap and drainage areas, a dose of 50 Gy/25 fractions/5 weeks, to receive a daily dose 2 Gy for 25 fractions in a 5 days a week schedule. The patients were treated on Equinox 80-E Cobalt-60 Teletherapy machine with gamma energy 1.25 MeV. Chest wall was treated with bilateral tangent pair technique, with a direct anterior field to the involved supraclavicular fossa.

During treatment, each patient was evaluated weekly till the end of treatment. Radiation effects on primary sites, lymph node drainage areas and irradiated normal tissue were carefully observed and charted. Radiation reactions observed were cutaneous reactions, esophagitis, shoulder movement restriction, pulmonary toxicity, rib fracture and brachial plexopathy. The local control of the tumour was assessed based on WHO criteria and toxicity graded according to RTOG criteria.

After the completion of treatment, all the patients were followed up every two weekly for one month and then, monthly up to a minimum of 6-months. At each followup each patient was assessed for subjective and objective improvement, radiation reactions, difficulty in swallowing, shoulder movements restriction, pulmonary toxicity and brachial plexopathy. Chest wall and lymph node drainage areas were carefully examined and reactions graded according to RTOG criteria.

**RESULTS:** The patient parameters were closely matched in two groups and their characteristics in Group I and II respectively were as follows: The median age (range) at presentation in Group I and II was: 48 (25-65) and 50 (30-67) years; Menopausal status: Premenopausal-15/30 (50%) vs. 8/30 (26.7%), postmenopausal-15/30 (50%) vs. 22/30 (73.3%); Rural background: 15/30 (50%) vs. 11/30 (36.7%), Urban background: 15/30 (50%) vs. 19/30 (63.3%); Common presenting complaints in Group I and II were: Lump in Breast-30/30 (100%) in both the groups, Lump in axilla-10/30 (33.3%) vs. 11/30 (43.3%), Bleeding and discharge from nipple-4/30 (13.3%) vs. 4/30 (13.3%), Skin changes-3/30 (10%) vs. 4/10 (13.3%); Smokers: 5/30 (16.7%) vs. 6/30 (20%); Karnofsky Performance Status (KPS): 80-13/30 (43.3%) vs. 12/30 (40%), 90-17/30 (56.7%) vs. 18/30 (60%).

The histopathology was infiltrating ductal carcinoma in all the patients in Group I and II. Site of primary tumour in Group I and II was: Right breast-10/30 (33.3%) vs. 14/30 (46.7%), Left breast- 20/30 (66.7%) vs. 16/30 (53.3%). Hormone receptor status in Group I and Group II was: Positive-12/30 (40%) vs. 18/30 (60%), Negative-18/30 (60%) vs. 12/30 (40%).

| Overall Stage | Group I 39 Gy/13#/3.1 wk. (n=30) No. of Patients (%) | Group II 50 Gy/25#/5 wk. (n=30) No. of Patients (%) | Overall (n=60) No. of Patients (%) | P value |
|---|---|---|---|---|
| IIA | 2(6.7%) | 0(0%) | 2(3.3%) | 0.150 |
| IIB | 11(36.7%) | 18(60%) | 29(48.3%) | 0.070 |

| | | | | |
|---|---|---|---|---|
| IIIA | 9(30%) | 6(20%) | 15(25%) | 0.371 |
| IIIB | 6(20%) | 4(13.3%) | 10(16.7%) | 0.488 |
| IIIC | 2(6.7%) | 2(6.7%) | 4(6.7%) | - |

***Table 1: Showing overall stage-wise (AJCC 2010) distribution at presentation***

All the patients completed their postoperative radiation treatment in the intended period. All patients tolerated radiotherapy well and there was no treatment interruption because of toxicity in both the groups.

The side effects were carefully documented during and after the treatment. The side effects of radiation therapy were graded as per RTOG criteria. Acute reactions and their grades in Group I and II were: Skin reactions, grade I-(21/30) 70% vs. (22/30) 73.3%, grade II-(7/30) 23.4% vs. (7/30) 23.4%, grade III-(1/30) 3.3% vs. (1/30)3.3%, grade IV-(1/30) 3.3% vs. nil; Oesophageal reactions; grade I-(7/30 ) 23.3% vs. (12/30) 40%, grade II-(3/30) 10% vs. nil. No patient in both the groups had grade III and IV oesophageal reactions.

The late side effects of radiation therapy were graded as per RTOG criteria. Late reactions and their grades in Group I and II were as follows: Skin toxicity: grade I-(12/30) 40% vs. (7/30) 23.3%, grade II-(4/30 ) 13.3% vs. (3/30) 10%; Oesophageal reactions: Grade I-(10/30) 33.3% vs. (6/30) 20%, grade II-(5/30) 16.7% vs. (4/30) 13.3%; Shoulder restriction: Grade I- (6/30) 20% vs. (9/30) 30%; grade II-nil; Pulmonary toxicity: Grade I: (2/30) 6.7% in both the groups, grade II-nil. No patient in both the groups experienced grade III and IV late radiation toxicities. All the late radiation reactions in Group I were higher than Group II, though not statistically significant.

Locoregional control after completion of radiotherapy in Group I vs. Group II were: Stage IIA: 1/2 (50%) vs. nil; Stage IIB: 10/11 (90.9%) vs. 17/18 (94.4%); Stage IIIA: 8/9 (88.9%) vs. 5/6 (83.3%); Stage IIIB-5/6 (83.3%) vs. 3/4 (75%); Stage IIIC-2/2 (100%) vs. 2/2 (100%) and all stages: 26/30 (86.7%) vs. 27/30 (90%). The local control rate between two groups was statistically not significant (p=0.796).

**Disease Status at Last Followup:**

| Status at last follow up | Group I 39 Gy/13#/3.1 wk. (n=30) | Group II 50 Gy/25#/5 wk. (n=30) | Overall (n=60) | P value |
|---|---|---|---|---|
| Local recurrence only | 2(6.7%) | 2(6.7%) | 4(6.7%) | - |
| Distant metastases only | 1(3.3%) | 0 | 1(1.7%) | 0.625 |
| Local recurrence + distant metastases | 1(3.3%) | 1(3.3%) | 2(3.3%) | - |
| No evidence of disease (NED) | 26(86.7%) | 27(90%) | 53(88.3%) | 0.797 |

***Table 2: Showing disease status at last followup***

Followup period ranged from 6 months to 18 months with a median followup of 10 months. At last followup, 6.7% patients had local recurrence only, in both the groups. One patient (3.3%) in Group I had distant metastases alone (stage IIB) and 1 patient each (3.3%) in both the groups (Stage IIB and IIIA) had both local recurrence and distant metastases. The local control rate between the two groups was not statistically significant (P=0.797).

**DISCUSSION:** Patients who present with locally advanced breast cancer (LABC) require multidisciplinary team approach that incorporates diagnostic imaging, surgery, chemotherapy and histopathological assessment, including molecular-based studies, radiation, and, if indicated, biologic and hormonal therapies.[1-3] The treatment outcome for an individual patient may be individualistic as per the expertise of the clinical oncologist and multidisciplinary approach is integrated. The introduction of adjuvant and neoadjuvant chemotherapy and hormone therapy regimens has significantly improved the prognosis of LABC.[4-6]

The current study was prospective in nature and was almost even in distribution of the tumour and clinical characteristics in both the groups; it confirmed the feasibility of hypofractionated radiotherapy in postoperative breast cancer patients and comparability in terms of local control and toxicities.

The impact of post mastectomy radiation therapy on local control and overall survival was supported by the results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), meta-analysis of 78-prospective randomised clinical trials. These trials investigated mastectomy with and without postoperative radiotherapy, the addition of post mastectomy radiation therapy provided similar proportional reductions in local recurrence regardless of patient age, tumour characteristics, use of systemic therapy, although the absolute risk reduction was larger in the higher-risk populations. The 5-year local recurrence risks in lymph node negative patients with and without post mastectomy radiation therapy were 2% and 6%, respectively, with a 3.6% decrement in 15-year breast cancer mortality. In lymph node positive patients, the 5-year

local recurrence risks were 6% and 23% respectively, which translated into a 5.4% benefit in 15-year breast cancer mortality.[7-12]

The Danish trial 82b initially reported a statistically significant improvement in rates of local recurrence (32% vs. 9%, P<.0001), disease-free survival (DFS) (34% vs. 48%, P<.001), and overall survival (OS) (45% vs. 54%, P<.001) in favour of chest wall and regional lymphatic irradiation plus cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy compared with CMF alone. Multivariate analysis confirmed that irradiation after mastectomy was a statistically significant factor in improving DFS and OS rates. This finding was consistent regardless of tumour size, number of positive lymph nodes, or tumour grade, and was upheld with longer followup.[13,14]

The study by El Sayed et al stated that hypofractionated radiation was safe and showed acceptable toxicity rate. Incidence of late skin toxicity and radiation induced pneumonitis were comparable between hypofractionated and conventional radiation arms.[15-17] These results are matched with our study results as both the arms had similar toxicity profile.

Eldeeb et al compared three fractionation schedules in post mastectomy patients enrolled into three groups. Although acute skin reactions were higher in the hypofractionated arms, there was no significant difference in the local recurrence rates or late radiation effects.[18] These results are consistent with our study results as there was no difference in toxicity and local control between the groups.

A retrospective analysis was done on 133 post-mastectomy patients treated with hypofractionated radiotherapy (HFRT) to determine whether hypofractionated radiotherapy yields acceptable efficacy and toxicity. Patients were treated with 40 Gy in 16 daily fractions. The median followup period was 5.03 years. Three patients had local recurrence as a first event, resulting in 5-year local recurrence-free survival of 97.6%. Five-year overall survival and 5-year breast cancer survival were 74.7% and 77.7% respectively.[19] These results are in concurrence with our study results, as both the arms had acceptable toxicity and efficacy.

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 local regional tumour relapse, late normal tissue effects and quality of life in 2236-women with early breast cancer (EBC) after primary surgery. The rate of local-regional tumour relapse was 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. It was concluded that a lower total dose in a small number of fractions could offer similar rates of tumour control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions.[20,21] Our study results in terms of loco regional failure are similar to the results of START trials, as both the groups showed statistically insignificant difference.

The efficacy of hypofractionated radiotherapy (HFRT) and conventional radiotherapy (CRT), was compared and observed that patients who received HFRT had significant increase in 5 year overall survival 62.7% and 73% in CRT and HFRT arms respectively.[22] Similar 5-year tumour free survival rates were seen by the conventional fractionation and hypofractionation.[16] Another study have shown that, hypofractionated (HF) group had comparable 4-year overall survival (OAS) rate with conventional fractionation (CF) group 96% versus 100%.[17]

**CONCLUSION:** In this present study almost similar results were seen in both the groups in terms of local control and side effects. However, acute and late reactions in the hypofractionation group (Group I) were higher than in the conventional fractionation group (Group II). Conventional fractionation schedule has got the disadvantage of extending the treatment for 5-weeks, which is inconvenient to the patient and utilises limited radiation resources in a busy radiotherapy centre, resulting in long waiting list. Whereas hypofractionated schedules have shown same response in terms of tumour control and late normal tissue effects with the advantage of decreased workload, increased compliance and reduced cost of treatment, it can be considered as a reliable alternative in radiation treatment for post mastectomy breast cancer patients.

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