

## **Hypofractionation in Breast Cancer - A Retrospective Study in a Tribal Population Based Medical College in West Bengal, India**

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### **Authors' contributions**

*This work was carried out in collaboration with all authors. Author SA designed the study and wrote the first draft of the manuscript. Author BG collected and tabulated the data and performed the statistical analysis. Author SB managed the literature searches and revised the manuscript during the course of peer-review. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Introduction:** In a tribal population based area in West Bengal, India though carcinoma cervix is the commonest malignancy in female patients, yet apart from that carcinoma breast is also increasing in number in the recent years. Breast cancer accounts for approximately 26.6% of female malignancy in the radiation oncology out-patient-department of our teaching hospital.

**Aims and Objectives:** To compare conventional RT regimen (50 Gy in 25 fractions over 5 weeks) with one hypofractionated regimen (40Gy in 15 fractions over 3 weeks) in stage II & stage III breast cancer patients as adjuvant radiation therapy in terms of local control, survival and adverse reactions.

**Materials and Methods:** It is a retrospective study which has been conducted in the department of Radiotherapy in BSMC (Bankura Sammilani Medical College) spanning from May 2012 to April 2017. A total number of patients included in this study was 302, out of which thirty six patients failed to follow up. So total of 266 patients included in the study were all histologically proved

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carcinoma breast treated surgically (97.74% by MRM & rest by BCS) with curative intent following which RT was used as adjuvant therapy. In one group (consisting of 133 patients) conventional regimen (50Gy in 25 fractions) was used. In another group (consisting the other 133 patients) dose-schedule used was a hypofractionated one i.e. 40Gy in 15 fractions. Dose per fraction in the 1st group was 2 Gy whereas in 2nd group it was 2.66 Gy. In all patients, RT was given in 5 days a week. Systemic therapy was administered as and when indicated.

**Results:** 4-year disease-free-survival (DFS) in conventional group was 78.94% and in hypofractionated group was 82.70%, (p value >0.05). 4-year overall survival (OS) in conventional group was 81.20% & in hypofractionated group was 85.70%, (p value >0.05). While adverse reactions in terms of both acute & chronic radiation toxicities were considered, there was no significant difference in between the two groups.

**Conclusion:** There is no significant difference between the conventional regimen and this hypofractionated regimen in terms of OS DFS & adverse reactions in this tribal-based Indian population. Hence, in our institution, we usually prefer Hypofractionated radiotherapy (40Gy/15 fractions) in adjuvant settings for breast cancer patients.

*Keywords: Hypofractionation; breast cancer; Ca breast.*

## 1. INTRODUCTION

As we are aware of the fact that radiotherapy is a mandatory modality in the course of treatment for Carcinoma of Breast, various dose prescriptions aside the conventional one had also been tried in particularly adjuvant setting [1]. The goal was to find out an optimum dose prescription by dint of which adequate local control could be achieved respecting the acute and late toxicities. Though breast cancer awareness programs and thorough screening have succeeded enough in developed countries in terms of early diagnosis, in developing countries like India diagnosis at an early stage and early commencement of treatment remain still a challenge [2]. Our practice domain includes a rural-based area i.e. Bankura in West Bengal, India where carcinoma cervix is still the commonest malignancy followed by ca breast as the second commonest malignant entity in the female population. But according to the records of recent years preserved by the Department of Radiation Oncology of Bankura Sammilani Medical College & Hospital, an increase in the incidence of breast cancer is a burning fact. Currently, breast cancer accounts for 26.6% of female malignancies in this area, as recorded, majority of which presented as Locally Advanced Breast Cancer (LABC), with AJCC stage T2 - 4, any N. As recommended, multidisciplinary approach including neoadjuvant chemotherapy (NACT), surgery, adjuvant radiotherapy, adjuvant chemotherapy, hormonal therapy and immunotherapy form the lines of treatment considering all patient factors, disease factors and treatment factors. Modified radical mastectomy (MRM) dominates over Breast

Conservation Surgery (BCS) with a statistic of 97.74% vs. 2.26% [3]. Due to the belief that removal of the entire diseased breast is mandatory to cure cancer they always opted for MRM even in those favourable cases where BCS might be a better option in term of cosmesis. However our study dealt with adjuvant radiotherapy, which was aimed to compare the so-called conventional breast RT regimen (50 Gy in 25 fractions over 5 weeks) with one hypofractionated regimen (40Gy in 15 fractions over 3 weeks) in stage II & stage III breast cancer patients as adjuvant therapy in terms of local control, survival and adverse reactions.

## 2. MATERIALS AND METHODS

### 2.1 Patients and Methods

In this single institutional retrospective study total 302 consecutive patients who got registered between May 2012 and April, 2017 in the outpatient department of Radiotherapy in BSMC(Bankura Sammilani medical college and Hospital) were included. Out of which thirty six patients failed to follow up; so total 266 patients were included in the study finally. After clinical evaluation including local and locoregional examination of bilateral breast and axillae a complete mammogram with proper BIRADS scoring was done. It was followed by a tru-cut biopsy confirming the pathological diagnosis of invasive breast cancer. As fine needle aspiration cytology sample does not suffice to perform immunohistochemistry, tru-cut biopsy was a mandatory inclusion criteria. It was followed by immunohistochemistry stating the oestrogen and progesterone receptor status and HER2 neu

amplification status too. Ki 67 was not routinely done in our public hospital before 2014, hence Modified Nottingham Prognostic Index (NPI) Scoring was considered significant to determine the grade of aggressiveness of the infiltrative carcinoma. It was followed by complete metastatic workup including a digital chest X ray sometimes an additional Contrast Enhanced Computed Tomography (CECT) Scan of Thorax, a CECT Scan of the whole abdomen. A Magnetic Resonance Imaging of brain was performed in symptomatic patients with the suspicion of brain metastasis. Patients who were clinical, AJCC anatomic prognostic stage group IIA, IIB, IIIA, IIIB and IIIC were included. Simply, T-stages included were T2- T4 and N-staged included were N0-N3. Significant baseline characteristics used for 1:1 patient matching included history regarding age (<50 years vs. >50 years; no more than 3 years apart), menopausal status (premenopausal vs. postmenopausal), number of relatives affected (1st degree vs. 2nd degree vs. no family history). BRCA 1 and BRCA 2 mutation analysis was not routinely done in our institution. Disease-related factors for patient matching were T-stage, N-stage, AJCC Prognostic stage group, NPI Score, status of post-surgery histopathological examination (HPE) report, ypT and ypN status as patients received Neo Adjuvant Chemotherapy regimens, Hormonal Receptor status, Her-2neu status etc. Other minor factors like age at first child birth (no more than 2 years apart), duration of breastfeeding (obtained from parity), the month that patients received the treatment in question i.e. radiation therapy (no more than 6 months apart) were attempted to match afterwards.

## 2.2 Treatment Protocol

For selected patients with early breast cancer (EBC) and Large Operable Breast Cancer (LOBC) who were referred for NACT from department of surgery and all LABC patients proper pre-treatment work up including complete blood count, kidney function test, liver function test, diabetic profile, serology and cardiological fitness including echocardiography and electrocardiogram was done. These patients received Taxane based (majority) or Anthracycline Based NACT regimens to achieve downstaging depending on the immunohistochemistry report obtained from true-cut biopsy paraffin blocks. After 14 days following the completion neo-adjuvant chemotherapy the patient was assessed for radical intervention i.e. modified radical

mastectomy (MRM) or BCS. After surgery histopathological examination reports were scrutinised for indications for Post Mastectomy Radiation Therapy (PMRT). Finally, adjuvant radiation was planned. All these patients were subdivided into two Groups on the basis of radiation dose-fractionation. The first group was treated with adjuvant Radiation Therapy (RT) with 50Gy in 25 fractions over 5 weeks, i.e. conventional fractionation; while the other group received 40Gy in 15 fraction over 3 weeks, i.e. hypofractionation. Dose per fraction were 2 Gy and 2.66 Gy, respectively. Adjuvant chemotherapy, Hormonal therapy, and Her-2 directed biologic therapy were administered as and when applicable abide by standard evidence-based guidelines. Follow up was done three months according to our institutional protocol. Further treatment included lines of chemotherapies and palliation.

## 2.3 Response Assessment

After completion of radiation therapy, clinical examination of bilateral breasts and axilla and high-resolution ultrasonography of ipsilateral chest flap, contralateral breast and bilateral axillae was done after 2 months. A chest X-ray and a CECT whole abdomen was done 3 monthly. MRI brain was performed on the basis of presenting symptoms as and when required. RECIST v1.1 criteria was used to determine complete response (CR), progressive disease (PD), partial response (PR) or stable disease (SD) in consequent follow ups after completion of treatment. Radiation toxicities (both acute and late) were assessed using RTOG (Radiation Therapy Oncology Group) toxicity grading. Median disease-free survival (DFS) or progression-free survival (mPFS) and overall survival (OS) were analysed using Kaplan-Meier survival over a median follow up of 60 months.

## 2.4 Statistical Analysis

SPSS statistical software version 17 (IBM Corp., Chicago, IL, USA) was used for data analysis. Quantitative data were presented by mean or median as appropriate, and qualitative data were presented as a percentage. OS and PFS/DFS were analysed by the Kaplan-Meier method and compared between both groups by log rank test ( $p=0.05$ ). The Cox proportional hazards model was used to adjust all prognostic factors. A 2-sided  $p$ -value  $<0.05$  was considered statistically significant.

### 3. RESULTS

In this rural population-based retrospective study a total number of patients included was three hundred two (302). Thirty six patients (36) failed to follow up. Hence, finally two hundred sixty six patients (266) were evaluated for this study (n = 266). They have been divided into two groups namely A & B. each containing 133 patients (n 133). 1:1 patient matching was done considering the criteria mentioned previously. In Group A conventional fractionation radiation therapy (CFRT) i.e. 50Gy in 25 fractions over 5 weeks was administered and in Group B hypofractionation radiation therapy (HFRT) i.e. 40Gy in 15 fractions over 3 weeks dose-schedule was used as adjuvant treatment. Electron boost (10 to 15 Gy) was done to the tumour bed where Breast conservation (BCS) performed (though in 2.26% patients only) as primary surgical modality. Acute & chronic reactions were noted and recorded during & at the completion of radiotherapy & in subsequent follow ups. Locoregional recurrence (LRR) & Overall survival (OS) & Disease-free survival (DFS) were also documented. MRM was performed in 96.99% and 97.74% of patients and BCS was

done in 3.01% and 2.26% followed by boost in Group A and Group B, respectively. Most common histopathological variety was Infiltrating duct carcinoma (84.96% in Group A and 88.72% in Group B). Neoadjuvant chemotherapy was administered in all cases. Taxol based chemotherapy was used in 90.22% and 90.97% patients in Group A & in Group B, respectively. Table 1 depicts patient characteristics and disease-related factors separately for Group A and Group B.

There was no significant difference between two Groups regarding radiation toxicity. Most common acute toxicity was skin reactions. RTOG GRADE 1 skin reactions occurred in 62.4% patients in Group A & 60.15% patients in Group B. GRADE 2 of the same was evident in 37.59% (for Group A) & 39.85% (fr Group B). No grade 3 skin toxicity was noted (p-value >0.05 i.e. not statistically significant).

As recorded, GRADE 1 chronic skin reactions evident in Group A was 51.87% and in Group B it was 53%. GRADE 2 of the same reaction was seen in 42.10% (Group A) & 50.36% (GroupB) ;p value >0.05 (Table 2).

**Table 1. List of patient characteristics attributed during study**

Patient characteristics	Patient group	
	A (CFRT)	B (HFRT)
Median age	46 years	50 years
Tumor size	T2	43(32.3%)
	T3	82(61.7%)
	T4	8(6.01%)
Lymph node status	N1	42(31.57%)
	N2	84(63.1%)
	N3	7(5.33%)
Types of surgery	MRM	130(97.74%)
	BCS	3(2.26%)
Histopathology	IDC	118(88.7%)
	ILC	12(9.0%)
	DCIS	3(2.2%)
Neoadjuvant chemotherapy	Taxol-based	121(90.97%)
	Non-Taxol	12(9.02%)
Receptor status	ER-ve	61(46.86%)
	ER+ve	72(54.13%)
	PR-ve	79(59.39%)
	PR+ve	54(40.60%)
Her2/neu	+ve	40(30.07%)
	-ve	54(40.60%)
	Unknown/equivocal	39(29.33%)

CFRT: Conventional fractionation radiation therapy, HFRT: Hypofractionation radiation therapy, MRM: Modified radical mastectomy, BCS: Breast conservation surgery, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, DCIS: Ductal carcinoma in situ

From the statistical point of view, 4 year local control for the conventional Group (CFRT; Group A) is 86.46% and for the hypofractionated Group (HFRT; Group B) is 90.6% (p value >0.05 ). 4 year overall survival in group A is 81.20% and in Group B it is 85.70% (p value >0.05). 4 year Disease-free survival in group A is 78.94 % and in Group B is 82.70% (p-value >0.05) (Table 3).

So on the basis of OS, DFS & locoregional recurrence, there are no statistically significant differences lies between the two Groups.

Fig. 1 shows a graphical representation of the probability of subclinical breast tumour control and normal tissue toxicity with increasing dose in Gy.

**Table 2. Percentage of occurrence of skin reaction and chronic reactions in patients**

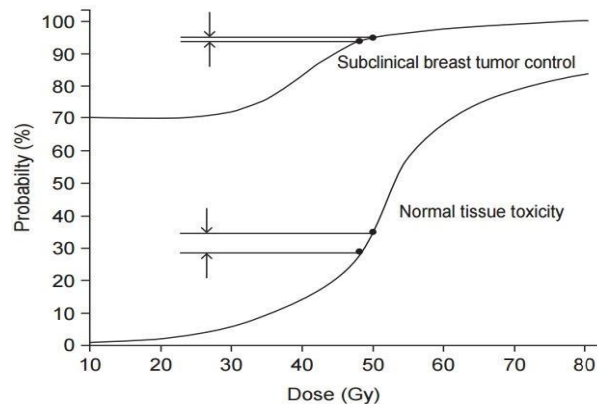
Patient characteristics		Patient group	
		A (CFRT)	B (HFRT)
<b>Skin Reactions (ACUTE)</b>	GRADE 1	50(39.59%)	53(39.8%)
	GRADE 2	83(62.40%)	80(60.2%)
	GRADE 3	0	0
(p>0.05)			
<b>Subcutaneous Tissue</b>	GRADE 1	71(53.38%)	69(51.87%)
	GRADE 2	62(46.62%)	64(48.12%)
	GRADE 3	0	0
(p>0.05)			
<b>Chronic Reactions</b>	GRADE 0	6(4.5%)	5(3.75%)
	GRADE 1	74(55.6%)	67(50.3%)
	GRADE 2	50(37.6%)	53(39.84%)
	GRADE 3	3(2.2%)	8(6.1%)
(p>0.05)			

CFRT: Conventional fractionation radiation therapy, HFRT: Hypofractionation radiation therapy

**Table 3. Data analysis showing significant relationship**

Patient Characteristics		Patient group	
		A (CFRT)	B (HFRT)
<b>Overall survival</b>	4-YEAR	108(81.20%)	114(85.7%)
(p>0.05)			
<b>Disease free survival</b>	4-YEAR	105(78.94%)	110(82.71%)
(p>0.05)			
<b>Locoregional control</b>	4-YEAR	105 (78.94%)	110(82.71%)
(p>0.05)			

CFRT: Conventional fractionation radiation therapy, HFRT: Hypofractionation radiation therapy



**Fig. 1. Probability of subclinical breast tumour control and normal tissue toxicity**

#### 4. DISCUSSION

Hypofractionation in Carcinoma Breast was cultivated by several study groups from time to time. Whelan et al. [4] conducted Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer study to determine whether a hypofractionated 3-week schedule of whole-breast irradiation is as effective as a 5-week schedule. Women with invasive breast cancer who had undergone breast-conserving surgery and in whom resection margins were clear and axillary lymph nodes were negative were randomly assigned to receive whole-breast irradiation either at a standard dose of 50.0 Gy in 25 fractions over a period of 35 days (the control group) or at a dose of 42.5 Gy in 16 fractions over a period of 22 days (the hypofractionated-radiation group). The study concluded, at 10 years, 71.3% of women in the control group as compared with 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, -6.9 to 9.8) [4].

Between 1998 and 2002, 2236 women with early breast cancer (pT1-3a pN0-1 M0) at 17 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy versus 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3.0 Gy over 5 weeks. 749 women were assigned to the 50 Gy group, 750 to the 41.6 Gy group, and 737 to the 39 Gy group. After a median follow up of 5.1 years (IQR 4.4–6.0) the rate of local-regional tumour relapse at 5 years was 3.6% (95% CI 2.2–5.1) after 50 Gy, 3.5% (95% CI 2.1–4.3) after 41.6 Gy, and 5.2% (95% CI 3.5–6.9) after 39 Gy. The estimated absolute differences in 5-year local-regional relapse rates compared with 50 Gy were 0.2% (95% CI -1.3% to 2.6%) after 41.6 Gy and 0.9% (95% CI -0.8% to 3.7%) after 39 Gy. Photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy, with an HR for the late change in breast appearance (photographic) of 0.69 (95% CI 0.52–0.91,  $p=0.01$ ). The study concluded the data are consistent with the hypothesis that breast cancer and the dose-limiting normal tissues respond to cancer and the dose-limiting normal tissues respond similarly to change in radiotherapy fraction size. 41.6 Gy in 13 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of local-regional tumour control [5].

Study conducted to test the benefits of radiotherapy schedules using fraction sizes larger than 2.0 Gy in terms of local-regional tumour control, normal tissue responses, quality of life, and economic consequences in women prescribed post-operative radiotherapy. 2215 women with early breast cancer (pT1-3a pN0-1 M0) at 23 centres in the UK were randomly assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 40 Gy in 15 fractions of 2.67 Gy over 3 week. 1105 women were assigned to the 50 Gy group and 1110 to the 40 Gy group. After a median follow up of 6.0 years (IQR 5.0-6.2) the rate of local-regional tumour relapse at 5 years was 2.2% (95% CI 1.3-3.1) in the 40 Gy group and 3.3% (95% CI 2.2 to 4.5) in the 50 Gy group, representing an absolute difference of -0.7% (95% CI -1.7% to 0.9%)—ie, the absolute difference in local-regional relapse could be up to 1.7% better and at most 1% worse after 40 Gy than after 50 Gy. The study interpreted 1105 women were assigned to the 50 Gy group and 1110 to the 40 were assigned to the 50 Gy group and 1110 to the 40 Gy group. After a median follow up of 6.0 years (IQR 5.0-6.2) the rate of local-regional tumour relapse at 5 years was 2.2% (95% CI 1.3-3.1) in the 40 Gy group and 3.3% (95% CI 2.2 to 4.5) in the 50 Gy group, representing an absolute difference of -0.7% (95% CI -1.7% to 0.9%)—ie, the absolute difference in local-regional relapse could be up to 1.7% better and at most 1% worse after 40 Gy than after 50 Gy [6].

Owen JR in his randomized trial, tested whether fewer, larger fractions were at least as safe and as effective as standard regimens. In this analysis, also assessed the long-term results of tumour control in the same population. In this study 1410 women with invasive breast cancer (tumour stage 1-3 with a maximum of one positive node and no metastasis) who had had local tumour excision of early-stage breast cancer were randomly assigned to receive 50 Gy radiotherapy given in 25 fractions, 39 Gy given in 13 fractions, or 42.9 Gy given in 13 fractions, all given over 5 weeks. The primary endpoint was a late change in breast appearance, which has been reported elsewhere. 1410 women with invasive breast cancer (tumour stage 1-3 with a maximum of one positive node and no metastasis) who had had local tumour excision of early stage breast cancer to receive 50 Gy radiotherapy given in 25 fractions, 39 Gy given in 13 fractions, or 42.9 Gy given in 13

fractions, all given over 5 weeks. The primary endpoint was late change in breast appearance, which has been reported elsewhere. The study concluded Breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues [7].

Yarnold et al. [8] in his study randomized one thousand four-hundred and ten women with T1-3 N0-1 M0 invasive breast cancer into one of three radiotherapy regimens after local tumour excision of early stage breast cancer; 50 Gy in 25 fractions (F) vs two dose levels of a test schedule giving 39 or 42.9 Gy in 13 F over 5 weeks. Fraction sizes were 2.0, 3.0 and 3.3 Gy, respectively. After a minimum 5-year follow up, the risk of scoring any change in breast appearance after 50 Gy/25 F, 39 Gy/13 F and 42.9 Gy/13 F was 39.6, 30.3 and 45.7%, from which an alpha/beta value of 3.6 Gy (95% CI 1.8-5.4) is estimated. The alpha/beta value for palpable breast induration was 3.1 Gy (95% CI 1.8-4.4). the study concluded An alpha/beta value of around the study concluded An alpha/beta value of around 3 Gy for late normal tissue changes in the breast is derived from the estimated equivalence of 41.6 Gy in 13 fractions and 50 Gy in 25 fractions over 5 weeks, in line with trial predictions [8].

Sanz [9] conducted a study to analyze the results of weekly hypofractionated treatment in 486 elderly patients with associated diseases that modify their performance status and do not tolerate long periods of daily irradiation. They were treated with conservative surgery or mastectomy and then adjuvant hypofractionated irradiation, administering 5 Gy or 6.25 Gy in 6 fractions, once a week (total dose 30–37.5 Gy) over 6 weeks. The study concluded once-weekly hypo-fractionated radiotherapy is a feasible and convenient option for elderly patients with breast cancer. It is a safe treatment modality with similar survival and local control results compared to standard fractionation, while the side effects are acceptable [9]

Sun et al. [10] and Team conducted a phase III noninferior randomized trial to evaluate the efficacy and toxicity of HFRT after mastectomy. In this analysis, 820 high- risk patients mainly with stage III breast cancer were enrolled and followed up for 5 years. Patients were randomly assigned after mastectomy to receive either HFRT (43.5 Gy/15f/3w) or CFRT (50 Gy/25f/5w) to the chest wall and supraclavicular nodal region. The primary endpoint was loco-regional

recurrence (LRR). The study reported that there were no significant differences in 5-year LRR (8.4% vs. 6.0%, P Z 0.396), DM (21.3% vs. 24.3%, P Z 0.530), DFS (75.1% vs. 74.6%, P Z 0.841), and OS (84.9% vs. 87.1%, P Z 0.562) between HFRT and CFRT group and concluded In patients with high-risk breast cancer after mastectomy, 43.5 Gy delivered in 15 fractions over 3 weeks has comparable efficacy and toxicity at 5 years with standard fractionation [10].

Randomized controlled trials of altered fraction size versus conventional fractionation for radiation therapy in women with early breast cancer who had undergone breast-conserving surgery. 8228 women in nine studies were analysed. altered fraction size (delivering radiation therapy in larger amounts each day but over fewer days than with conventional fractionation) did not have a clinically meaningful effect on: local recurrence-free survival (Hazard Ratio (HR) 0.94, 95% CI 0.77 to 1.15, 7095 women, four studies, high-quality evidence), cosmetic outcome (Risk ratio (RR) 0.90, 95% CI 0.81 to 1.01, 2103 women, four studies, high-quality evidence) or overall survival (HR 0.91, 95% CI 0.80 to 1.03, 5685 women, three studies, high-quality evidence). Acute radiation skin toxicity (RR 0.32, 95% CI 0.22 to 0.45, 357 women, two studies) was reduced with altered fraction size. Altered fraction size was associated with less patient-reported ( $P < 0.001$ ) and physician-reported ( $P = 0.009$ ) fatigue at six months (287 women, one study). The review concluded altered fraction size regimens (greater than 2 Gy per fraction) does not have a clinically meaningful effect on local recurrence, is associated with decreased acute toxicity and does not seem to affect breast appearance, late toxicity or patient-reported quality-of- life measures for selected women treated with breast conserving therapy [11].

The randomized trial was from the MD Anderson Cancer Center, in Houston. The study was conducted in 287 women aged 40 years and older with early- stage breast cancer (stage 0-2), who were randomly assigned to receive either HF-WBI (42.56 Gy in 16 fractions of WBI;  $n = 138$ ) or CF-WBI (50.00 Gy in 25 fractions of WBI;  $n = 149$ ). The rate of physician- assessed toxicity of grade 2 or higher was significantly lower for women receiving HF-WBI (47% vs

78%;  $P < .001$ ), as were acute toxic effects of grade 3 or higher (0% vs 5%;  $P = .01$ ). In particular, rates for physician-assessed fatigue, pruritus, breast pain, and dermatitis were significantly lower for women receiving HF. Although patient-reported quality of life, as reported from the Functional Assessment of Cancer Therapy for Patients with Breast Cancer, was similar for women receiving HF and CF, items associated with lack of energy and trouble meeting family needs favoured women receiving HF. The study concluded treatment with HF-WBI appears to yield lower rates of acute toxic effects than CF-WBI as well as less fatigue and less trouble meeting family needs 6 months after completing radiation therapy [12].

A task force authorized by the American Society for Radiation Oncology weighed evidence from a systematic literature review and produced the recommendations contained herein. The majority of patients in randomized trials were aged 50 years or older, had disease Stage pT1-2 pN0, did not receive chemotherapy, and were treated with a radiation dose homogeneity within  $\pm 7\%$  in the central axis plane. Such patients experienced equivalent outcomes with either HF-WBI or CF-WBI. Patients not meeting these criteria were relatively underrepresented, and few of the trials reported subgroup analyses. For patients not receiving a radiation boost, the task force favoured a dose schedule of 42.5 Gy in 16 fractions when HF-WBI is planned. The task force also recommended that the heart should be excluded from the primary treatment fields (when HF-WBI is used) due to lingering uncertainty regarding late effects of HF-WBI on cardiac function. Data were sufficient to support the use of HF-WBI for patients with early-stage breast cancer who met all the aforementioned criteria. For other patients, the task force could not reach agreement either for or against the use of HF-WBI, which nevertheless should not be interpreted as a contraindication to its use [13].

Chan et al. [14] conducted a study to determine if there is an increase in hospital-related morbidity from cardiac causes with HF-WBI relative to CF-WBI. Between 1990 and 1998, 5334 women  $\leq 80$  years of age with early-stage breast cancer were treated with postoperative radiation therapy to the breast or chest wall alone. A population-based database recorded baseline patient, tumour, and treatment factors. The median follow-up was 13.2 years. For left-sided cases, 485 women were treated with CF-

WBI, and 2221 women were treated with HF-WBI. The 15-year cumulative hospital-related morbidity from cardiac causes (95% confidence interval) was not different between the 2 radiation therapy regimens after propensity-score adjustment: therapy regimens after propensity-score adjustment: 21% (19-22) with HF-WBI and 21% (17-25) with CF-WBI ( $P = .93$ ). For right-sided cases, the 15-year cumulative hospital-related morbidity from cardiac causes was also similar between the radiation therapy groups ( $P = .76$ ). The study concluded there is no difference in morbidity leading to hospitalization from cardiac causes among women with left-sided early-stage breast cancer treated with HF-WBI or CF-WBI at 15-year follow-up [14].

Karasawa et al. [15] conducted study to evaluate the efficacy and safety of hypofractionated whole-breast irradiation (HF-WBI) compared with conventionally fractionated (CF) WBI. Patients with early breast cancer (stages 0- II and  $< 3$  positive lymph nodes) who had undergone breast-conserving surgery were eligible for the HF-WBI study. HF-WBI was administered at 43.2 Gy in 16 fractions over 3.2 weeks to the whole breast with an additional tumor-bed boost of 8.1 Gy in 3 fractions over 3 days for positive surgical margins or those  $< 5$  mm. CF-WBI was administered at 50 Gy in 25 fractions over 5 weeks to the whole breast with an additional tumor-bed boost of 16 Gy in 8 fractions over 1.4 weeks to 6 Gy in 3 fractions over 3 days, depending on margin status. Grade 2 acute skin reactions were observed for 24 patients (3%) in the HF-WBI group and 53 for 24 patients (3%) in the HF-WBI group and 53 patients (14%) in the CF-WBI ( $p < 0.001$ ) group. The median follow-up period was 27 months. Two cases of intrabreast tumor recurrence were observed in each treatment group. Regional lymph node recurrence was observed in 1 HF-WBI patient and 2 CF-WBI patients. The study concluded HF-WBI is superior to CF-WBI in terms of acute skin reaction and has the same short-term efficacy [15].

Kim et al. [16] in phase 2 trial of accelerated, hypofractionated whole-breast irradiation (AH-WBI) delivered as a daily dose of 3 Gy to the whole breast followed by a tumor bed boost. Two hundred seventy-six patients diagnosed with breast cancer (pT1-2 and pN0-1a) who had undergone breast-conserving surgery in which the operative margins were negative were treated with AH-WBI delivered as 39 Gy in 13 fractions of 3 Gy to the whole breast once daily



over 5 consecutive working days, and 9 Gy in 3 sequential fractions of 3 Gy to a lumpectomy cavity, all within 3.2 weeks. After a median follow-up period of 57 months (range: 27-75 months), the rate of 5-year locoregional recurrence was 1.4% (n=4), whereas that of disease-free survival was 97.4%. The mean pretreatment percentage breast retraction assessment was 12.00 (95% confidence interval [CI]: 11.14-12.86). The mean value of interval [CI]: 11.14-12.86). The mean value of percentage breast retraction assessment increased to 13.99 (95% CI: 12.17-15.96) after 1 year and decreased to 13.54 (95% CI: 11.84-15.46) after 3 years but was not significant ( $P > .05$ ). The study reported AH-WBI consisting of 39 Gy in 13 fractions followed by a tumor bed boost sequentially delivering 9 Gy in 3 fractions can be delivered with excellent disease control and tolerable skin toxicity in patients with early-stage breast cancer after breast-conserving surgery [16].

Bekelman et al. [17] conducted Retrospective, observational cohort study, in patients with incident early-stage breast cancer treated with lumpectomy and WBI from 2008 and 2013 and divided patient into 2 cohorts: (1) the hypofractionation-endorsed cohort (n = 8924) included patients aged 50 years or older without prior chemotherapy or axillary lymph node involvement and (2) the hypofractionation-permitted cohort (n = 6719) included patients younger than 50 years or those with prior chemotherapy or axillary lymph node involvement. Hypofractionated WBI increased from 10.6% (95% CI, 8.8%-12.5%) in 2008 to 34.5% (95% CI, 32.2%-36.8%) in 2013 in the hypofractionation- endorsed cohort and from 8.1% (95% CI, 6.0%-10.2%) in 2008 to 21.2% (95% CI, 18.9%-23.6%) in 2013 in the hypofractionation-permitted cohort. Adjusted mean total health care expenditures in the 1 year after mean total health care expenditures in the 1 year after diagnosis were \$28,747 for hypofractionated and \$31,641 for conventional WBI in the hypofractionation- endorsed cohort (difference, \$2894; 95% CI, \$1610- \$4234;  $P < .001$ ) and \$64,273 for hypofractionated and \$72,860 for conventional WBI in the hypofractionation- permitted cohort (difference, \$8587; 95% CI, \$5316- \$12,017;  $P < .001$ ). Adjusted mean total 1-year patient out-of-pocket expenses were not significantly different between hypofractionated vs conventional WBI in either cohort [17].

Deshmukh et al. [18] constructed a decision-analytic model that followed women who were treated with lumpectomy for early-stage breast cancer. Recurrence, mortality, complication rates, and utilities (five-year radiation-associated quality of life scores), were extracted from RCTs. Costs were based on Medicare reimbursement rates. HF-WBI dominated CF-WBI (ie, resulted in higher quality-adjusted life-years [QALYs] and lower cost) in all scenarios. HF-WBI also had a greater likelihood of cost-effectiveness compared with IORT; under a societal perspective that assumes that radiation-associated disutility persists, HF-WBI results in an ICER of \$17 024 per QALY compared with IORT with a probability of cost-effectiveness of 80% at the \$100 000 per QALY willingness-to-pay of 80% at the \$100 000 per QALY willingness-to-pay threshold. If radiation-associated disutility is assumed to discontinue, the ICER is lower (\$11 461/QALY), resulting in an even higher (83%) probability of relative cost-effectiveness. The ICER was most sensitive to the probability of metastasis and treatment cost. The study concluded, for women with early-stage breast cancer requiring adjuvant radiotherapy, HF-WBI is cost-effective compared with CF-WBI and IORT [18].

The result of our study clearly suggests that outcome for both dose schedule was equivalent. Hypofractionation is rather cost effective considering the low socio-economic status of our practice domain which reflects a major population of India.

## 5. CONCLUSION

There is no significant difference in between the conventional regimen and this hypofractionated regimen in terms of OS, DFS and adverse reactions. Hence, in our institution, we usually prefer Hypofractionated radiotherapy (40Gy/15 fractions) in adjuvant settings for breast cancer patients.

## CONSENT

All authors declare that written informed consent was obtained from each patient (or other approved relative).

## ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the

appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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