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ORIGINAL ARTICE

Evaluation of Three Weeks Hypofractionated Whole Breast Irradiation with a Sequential Boost in Breast Cancer Patients

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ABSTRACT

Background: Breast cancer is a common and a serious condition. Breast conserving surgery followed by radiation therapy is the recommended course of treatment for early breast cancer. While preserving comparable results, hypofractionation advances the treatment's cost-benefit ratio and reduces the waiting list. The study's goal was to determine whether hypofractionated whole breast irradiation with sequential boost and 15 treatment days was successful in treating early breast cancer. **Methods:** Patients were allocated into 2 Arms, Arm A (standard hypofractionation arm, whole breast irradiation HF-WBI 40Gy/15fractions followed by boost 10Gy/5 fractions) and Arm B (short hypofractionated arm, HF-WBI 36.63Gy/11followed by boost of 13.32Gy/ 4 fractions), with a same dose to the regional lymph nodes if there is indication in both arms. Patients were followed at 3, 6, 9 and 12 months after treatment and acute and chronic toxicity were recorded. **Results:** One hundred and twenty female patients were involved in the study. Between both groups, there was no statistically significant difference regarding acute toxicity (skin was the most frequently affected in both groups). Patients with grade 2 toxicity showed improvement over 3 months' period (from 23.33% to 10% in arm A and from 26.67% to 16.67% in arm B). Arm A had significantly lower skin toxicity than arm B over 12 months' follow up. No patients had any chronic laryngeal, cardiac or lung toxicity symptoms at 6, 9 and 12 months of follow-up. **Conclusions:** A shortened 3-week HF-WBI schedule has cost, and time benefit and it is as secure and effective with low toxicity as standard 4-weeks HF-WBI and can be a sensible treatment after breast conservation surgery.

Keywords: Hypofractionated, Radiotherapy, breast, sequential boost.

INTRODUCTION

The most common cancer in women and one of the main causes of death among them is breast cancer [1]. In less developed nations, breast cancer is the leading cause of cancer death among women, coming in second place only to lung cancer globally [2]. In clinical practice, breast-conserving surgery (BCS) followed by radiotherapy produced better outcomes in terms of local control, distant control, and overall survival than surgery alone [3]. Thus, radiation therapy and breast-conserving surgery were found to be the best way to treat early breast cancer [4]. With truly excellent local control rates of 90–95% following BCS, radiation therapy in the form of whole breast radiation therapy (WBRT) serves as the standard adjuvant therapy [5].

Reducing the time of treatment increases the financial feasibility and patient fulfillment for patients with early-stage breast cancer. Hypofractionated radiotherapy (HF-RT) is more cost- effective and less time consuming than conventional RT. In this way, numerous breast cancer patients favor HF-RT [6]. Recent randomized trials have affirmed that hypo-fractioned WBRT with a subsequent boost is equivalent to conventional WBRT with a consequent boost and is well-tolerated with regarding to local recurrence, toxicity and cosmetic results [7,8].

Hypofractionation results in reduced therapeutic expenses, patient visits to radiation facilities, machine load, and waiting lists for RT departments, all of which improve access to healthcare. There were no differences between the groups receiving HF-RT and conventional radiation doses in terms of local control, locoregional control, disease-free survival, or overall survival rates [9]. Several trials emerged to support hypofractionation radiation **(Table 1)**.

Based on a radiobiologic model, this hypofractionated approach delivers a higher dosage per fraction in fewer fractions (often with a lower total nominal dose) over a shorter period of time overall while still being at least as effective as the more conventional longer schedule [10].

The development of CT-based treatment planning and 3D conformal RT (3DCRT), which allows for exact target volume determination, dose distribution calculation, and virtual simulation [11], marked the beginning of an important and challenging phase in the RT technique. The dose distributions around the heart can be shaped using volumetric modulated arc therapy (VMAT) or intensity modulated radiation therapy (IMRT) approaches [12]. In the Helical TomoTherapy procedure, IMRT is given to a patient as they are moving along the axis of a megavoltage X-ray source, providing a special 360-degree rotational irradiation. There may be less uncertainty with this rotational administration method centered on a single "virtual isocenter" than with many patient shifts [13].

In order to improve patient quality of life and make more efficient use of time and resources, this study aims to assess the effectiveness of HF-WBI followed by sequential boost in a period of fifteen days in patients with early breast cancer who have undergone conservative breast surgery.

METHODS

A prospective clinical trial was carried out in clinical oncology and nuclear medicine department Zagazig University Hospitals, Egypt, from May 2020 to May 2022. Inclusion criteria for the study were histological diagnosis of unilateral breast carcinoma, histologically confirmed ductal carcinoma in-situ (DCIS) or invasive duct or invasive lobular carcinoma (IDC,ILC) in patients who underwent breast conservative surgery (lumpectomy/quadrantectomy) with early breast carcinoma (Stages 0-IIB), margins negative (no tumor on ink), not receiving radiotherapy previously, received adjuvant chemotherapy, hormone therapy was allowed, ECOG performance status of 0-2, and no serious non-malignant diseases (cardiovascular or pulmonary diseases), while exclusion criteria included breast mammography micro-calcifications before to initiating RT, lobular carcinoma in situ (LCIS) alone or non-breast epithelial histologically confirmed, multicentric disease, previous treatment for the other breast or synchronous contralateral breast cancer or if they had previous RT to the present breast, suspicious regional lymph nodes on the other side clinically or radiographically unless confirmed negative for malignancy, pregnancy, distant metastases, synchronous second primary cancer or comorbidity like: Collagen vascular disease, Paget's disease, and psychiatric or addiction that made informed consent impossible or lead to bad compliance and noncooperation.

Assuming that the rate of admission of females with breast cancer and fulfilling the inclusion criteria at the oncology department, Zagazig university, is 10 cases per month. So, a comprehensive sample of 120 patients were enrolled in the study. Patients were allocated into 2 Arms, Arm A (standard hypofractionation arm, whole breast irradiation HF-WBI 40Gy/15fractions followed by boost 10Gy/5 fractions) and Arm B (short course hypofractionation arm, HF-WBI 36.63Gy/11followed by boost of 13.32Gy/ 4 fractions), each of which compromise 60 patients had early-stage breast cancer and all patients get a boost. Written informed consent was obtained from all participants. The study was done according to The Code of Ethics of The World Medical Association (Declaration of Helsinki) for studies involving humans. The Study was also approved by our institutional review board (IRB, ##6262/14-7-2020).

Patients were subjected to pre, and post radiotherapy assessment and data collected included age, breast laterality, histology, tumor size, AJCC pathological tumor & nodal status, receptors status (ER, PR, HER2Neu), radiation target volume (whole breast or whole breast +regional LN), systemic treatment (adjuvant chemotherapy, hormonal treatment). Acute and late toxicity assessment were the primary end point in our study; secondary end point was assessment of dose constraints. Acute and late toxicities were scored using version 3.0 of RTOG/EORTC toxicity scale. Acute toxicity was evaluated after the end of radiotherapy and after 3 months, chronic toxicity was recorded after 6, 9 and 12 months of radiotherapy and was recorded from the

last examination. Follow up included a full clinical examination which was carried out at every assessment point, hematological and biochemical laboratory evaluation, tumor markers (CA 15-3), mammography, plain chest X-ray, pelviabdominal ultrasound, CT if needed, ECHO for left-sided breast cancer and bone scan if indicated.

Radiotherapy planning: In the supine position, simulation using computed tomography was performed. After the end of chemotherapy or within two months of the operation, 3DCRT treatment was initiated. A clinical target volume (CTV) was established by contouring the breast target volume. Tolerance dosages were used to limit the exposure to organs at risk. The tangent beams could not include more than 3 cm of lung at any level in beams eye views. Utilizing MLC should reduce the dose reaching the heart while maintaining target coverage. RNI was given together with an optional posterior axillary boost and anterior supraclavicular field. To limit brachial plexus dose, the dose in the breast CTV had to be between 95% and 105% of the prescribed dose and below 107% in the supraclavicular volume. To guarantee the proper dose, treatment dose-volume histograms were evaluated. To construct a boost planning target volume, the tumour bed was seen on computed tomography and contoured with a 1- to 2-cm margin. An isodose line that totally covered the planning target volume was given a boost dose prescription.

Statistical analysis was carried out with SPSS. Numbers and percentages were used to represent categorical data, whereas means, standard deviations, medians, and ranges were used to represent continuous data.

RESULTS

From May 2020 to May 2022, we enrolled 120 women who were divided into 2 arms. All of the women finished the protocol therapy and were included in the analysis.

Patient and tumor characteristics: Table (2) displays the study cohort's baseline characteristics. Twelve months were the median follow-up. In arm A, the median age at diagnosis was 46, but in arm B, it was 45. Grade 2 tumour were most frequently found. T2 tumors showed predominance, 66.67% in Arm A and 56.67% in Arm B. N1 tumors were found in 50% in arm A and 53.33% in arm B. Ki-67 expression was high in only 12 patients (20%) in arm A and 6 patients (10%) in arm B, the median Ki-67 index was 14%, which was used as the cut-off for low/high Ki-67 expression. Higher-risk patients were enrolled including 30(50%)and 26(43.33%) in arm A and B respectively with pathologically positive nodes who required regional nodal irradiation (RNI).

Dose constraints: Arm A patients had slightly larger breast volume. The mean doses of PTV in the patients were 98.82% and 99.73% of total dose in arm A and arm B respectively. The mean of V95% (breast volume that received 95% of the recommended dose) was 89.52%in arm A and 90.13% in arm B. On the other hand, the mean of V105% was observed in about 36.8% in arm A patients and in 37.08 in arm B patients. All values regarding organs at risk (OAR) were less than tolerated doses. The mean dose for ipsilateral lung was15.70Gy in arm A and 14.25Gyin arm B, while the heart had a mean of 3.87Gy in arm A and 1.45Gy. Mean value for V20 of the lung (volume of the lung receiving 20Gy) was 15.12% and 14.72% in arm A and B respectively, while V30 of the heart (volume of the heart receiving30Gy) was far less (2.86% and 2.51% in arm A and B respectively) **(Table 3)**.

Acute toxicity: Acute toxicity including erythema, edema, and desquamation, after the patient had been finished radiation and 3 months later, skin was the most frequently affected where 42 patients (70%) in arm A and 52 patients (86.67%)in arm B had skin manifestations at finishing, and 40 patients (66.67%)in arm A and 46 patients (76.67%) in arm B still had symptoms at 3 months after finishing. Grade 1 and 2 toxicity were dominant at the end of radiotherapy, however, patients with grade 2 toxicity showed improvement over 3 months period, i.e., there was significant improvement between time points (from 23.33% to 10% in arm A and from 26.67% to 16.67% in arm B). However, no statistical significance was detected when comparing both arms **(Table 4)**.

Chronic toxicity and lymphedema: Chronic toxicity, including hyperpigmentation and atrophy, after 6,9 and 12months later, skin was the most frequently affected. No patients had any chronic laryngeal, cardiac or lung toxicity symptoms at 6,9 and 12 months of follow-up. Thirty-two patients in arm A and 38 patients in arm B still had skin manifestations at 6 months follow up, however, they were all consistent mostly with G1 changes. There was highly significant improvement in Arm A compared to Arm B over 12 months' follow-up as only 12 patients in arm A still had G1 manifestation at 12 months after treatment while on the other hand 42 patients in arm B had persistent symptoms. **Table**

(5) shows details of chronic toxicity and **table (6)** showed lymphedema in studied patients.

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Table 1: Trials of hypofractionation

Trial No. of patients	*First author*	*Years*	*Median follow up (years)*	*Fractionation schedules*	*DFS*	*OS*	*Local control*
West Midlands (358)	Spooner	1985-1992	16.9	50Gy/25 fr 40Gy/15 fr	NS	NS	88.9% 86.2%
Royal Mardsenl/ Gloucestershire (1410)	Owen	1986-1998	9.7	50Gy/25 fr 39Gy/13 fr 39.9Gy/13 fr	NS	NS	87.9% 85.2% 90.4%
Ontario Oncology Group OCOG(1234)	Whelan	1993-1996	12	50Gy/25 fr 42.7Gy/15 fr	NS	84.4% 84.6%	93.3% 93.8%
START (A) (2236)	Haviland	1999-2002	9.3	50Gy/25 fr 39Gy/13 fr 41.6Gy/13 fr	86.4% 84.8% 88%	88.9% 89.3% 88.7%	96.4% 94.8% 96.5%
START (B) (2215)	Haviland	1999-2001	9.9	50Gy/25 fr 40Gy/15 fr	85.9% 89.4%	89% 92%	96.7% 97.8%
Fast Forward (4096)	-	2011-2014	3	40Gy/15 fr 27Gy/5 fr 26Gy/5 fr	94% 93.5% 92.8%	92% 92.3% 91.6%	97.3% 97.6% 98.1%
DBCG HYPO (1882)	Offersen	2009-2014	7.62	50Gy/25 fr 40Gy/15 fr	- -	93.4% 93.4%	96.7% 97%

Table 2: Tumour characteristics and treatment details

Variables	**Arm A**	**Arm B**	**P-value**
	n=60 (%)	*n=60 (%)*	
Tumour grade			
Grade 1	4(6.67%)	4(6.67%)	0.848
Grade 2	40(66.67%)	36(60%)	
Grade 3	16(26.66%)	20(33.33%)	
Tumour size			
T1	20 (33.33%)	26 (43.33%)	0.425
T1a	0(0%)	0(0%)	
T1b	0(0%)	0(0%)	
T1c	20(33.33%)	26(43.33%)	
T2	40(66.67%)	34 (56.67%)	
Nodal status			
N0	30(50%)	28(46.67%)	0.80
N1	30(50%)	32(53.33%)	
Ki-67			
Low	48(80%)	54(90%)	0.28
High	12(20%)	6(10%)	
Radiation Target Volume			
Whole Rt breast	20(33.33%)	26 (43.33%)	0.607
Whole Lt breast	10(16.67%)	8 (13.33%)	
Whole Rt+Supraclav LN	20(33.33%)	22(36.67%)	
Whole Lt+Supraclav LN	10(16.67%)	4(6.67%)	

Table 3: Treatment and dosimetric characteristics

Variables	Arm A	Arm B	P-value
	n=60 (%)	*n=60 (%)*	
Breast volume *(cc)*			
Mean±SD	1400.1±560.6	1384.4±550	0.913
Boost volume *(cc)*			0.178
Mean±SD	68±20.2	61±19.6	
PTV dose %			
Mean PTV dose *%(D mean)*			
Mean±SD	98.82±3.81	99.73±3.45	0.33
Maximum PTV Dose *%(D maximum)*			
Mean±SD	106.5±1.5	105.9±1.0	0.07
Minimum PTV Dose *%(D minimum)*			
Mean±SD	18.2±16.0	17.33±16.19	0.834
V95*(%)*	89.52±7.1	90.13±5.11	0.703
V105*(%)*	36.8±7.0	37.08±7.60	0.882
Ipsilateral Lung			
D mean *(Gy)*			
Mean±SD	15.70±2.31	14.25±3.41	0.058
D maximum*(Gy)*			
Mean±SD	40.41±1.13	37.89±0.64	**<0.01****
BED	76.73±3.17	81.05±2.22	**<0.01****
V20*(%)*			
Mean±SD	15.12±3.8	14.72±3.71	0.681
Heart			
D mean *(Gy)*			
Mean±SD	3.87±0.60	1.45±0.55	**<0.01****
BED	4.07±0.62	1.52±0.61	**<0.01****
D maximum *(Gy)*			
Mean±SD	6.30±0.69	2.77±0.72	**<0.01****
BED	7.19±0.89	3.13±0.93	**<0.01****
V30*(%)*			
Mean±SD	2.86±1.90	2.51±1.23	0.400

Table 4: Acute Toxicity after radiotherapy in the studied patients

Variables	Arm A	Arm B	P-value
	n=60 (%)	*n=60 (%)*	
Skin			
Erythema post radiotherapy			0.487
G0	16 (26.67%)	8(13.33%)	
G1	28 (46.67%)	30(50%)	
G2	14(23.33%)	16(26.67%)	
G3	2 (3.33%)	6(10%)	
G4	0(0%)	0(0%)	
Erythema after 3 months			0.490
G0	22(36.67%)	14(23.33%)	
G1	32(53.33%)	34(56.67%)	
G2	6(10%)	10(16.67%)	

Variables	Arm A	Arm B	P-value
	n=60 (%)	*n=60 (%)*	
G3	0(0%)	2(3.33%)	
G4	0(0%)	0(0%)	
Edema post radiotherapy			0.893
G0	40(66.66%)	38(63.33%)	
G1	16(26.67%)	16(26.67%)	
G2	4(6.67%)	6(10%)	
G3	0(0%)	0(0%)	
G4	0(0%)	0(0%)	
Edema after 3 months			0.810
G0	48(80%)	44(73.34%)	
G1	10(16.67%)	14(23.33%)	
G2	2(3.33%)	2(3.33%)	
G3	0(0%)	0(0%)	
G4	0(0%)	0(0%)	
Desquamation post radiotherapy			0.644
G0	18(30%)	12(20%)	
G1	26(43.34%)	26(43.33%)	
G2	14(23.33%)	16(26.67%)	
G3	2(3.33%)	6(10%)	
G4	0(0%)	0(0%)	
Desquamation after 3months			0.594
G0	22(36.66%)	18(30%)	
G1	34(56.67%)	32(53.34%)	
G2	4(6.67%)	8(13.33%)	
G3	0(0%)	2(3.33%)	
G4	0(0%)	0(0%)	

Table 5: Chronic Toxicity after radiotherapy in the studied patients

Variables	Arm A	Arm B	P-value
	n=60 (%)	*n=60 (%)*	
Hyperpigmentation			0.728
After 6 months			
G0	28(46.67%)	22(36.67%)	
G1	30(50%)	36(60%)	
G2	2(3.33%)	2(3.33%)	
G3	0(0%)	0(0%)	
After 9 months			0.30
G0	38(63.33%)	30(50%)	
G1	22(36.67%)	30(50%)	
G2	0(0%)	0(0%)	
G3	0(0%)	0(0%)	
After 12 months			0.09
G0	48(80%)	36(60%)	
G1	12(20%)	24(40%)	
G2	0(0%)	0(0%)	
G3	0(0%)	0(0%)	

Variables	Arm A	Arm B	P-value
	n=60 (%)	*n=60 (%)*	
Breast atrophy			
After 6 months			0.116
G0	40(66.67%)	42(40%)	
G1	18(30%)	32(53.33%)	
G2	2(3.33%)	4(6.67%)	
G3	0(0%)	0(0%)	
After 9 months			**0.021***
G0	46(76.67%)	26(43.33%)	
G1	14(23.33%)	30(50%)	
G2	0(0%)	4(6.67%)	
G3	0(0%)	0(0%)	
After 12 months			**0.017***
G0	56(93.33%)	38(63.33%)	
G1	4(6.67%)	20(33.33%)	
G2	0(0%)	2(3.33%)	
G3	0(0%)	0(0%)	

Table 6: Lymphedema after radiotherapy in studied patients

Variable	Arm A	Arm B	P-value
	n=60 (%)	*n=60 (%)*	
No arm Lymphedema	44(73.33%)	48(80%)	0.54
Arm Lymphedema stage 0-1	16(26.67%)	12(20%)	

Table 7: Locoregional and distant control in studied group

Variables	Arm A	Arm B	P-value
	n=30 (%)	*n=30 (%)*	
Locoregional & distant control after 12 months	30(100%)	30(100%)	1.00
Locoregional & distant control after 18 months	30(100%)	30(100%)	

DISCUSSION

When compared to standard HF-WBI, which delivers 40Gy in 15 fractions then boosts 10Gy in 5 fractions over a period of twenty treatment days, one of the shortest course of daily hypofractionated whole breast irradiation (HF-WBI) was performed in our study, evaluating 36.63Gy in 11 fractions to the whole breast followed by a sequential boost of 13.32Gy in 4 fractions over a total of fifteen treatment days. Sequential boost was chosen for our study because to its familiarity, ease of usage, and flexibility in boost strategy. Our results appear to support the idea that the well-known radiobiological features of breast cancer continue to hold steady in the 2- to 5-Gy fraction range and that iso-effective doses can be anticipated to continue being iso-effectively across a variable risk groups.

Current HF-WBI courses take four weeks or more to finish, reduced from 6 to 7weeks with conventional fractionated whole breast irradiation (CF-WBI) and boost. Decreasing the time of the course of adjuvant breast radiation increases patient comfort, fulfillment, and ability, enabling to resume work promptly, more access to breast radiotherapy, consequently, breast conservation, while lowering health care economies [14,15].

The Canadian and United Kingdom trials did not consistently allow or reject a boost, in contrast to our HF-WBI course where a lumpectomy boost was required to be administered. Nandi et al.'s [16] experience with START B fractionation, which involved boost in BCS patients, was described in detail. In a patient population that was fairly diverse, the investigators documented minimal toxicity rates.

After BCS, women who refused routine fractionation were treated with HF-WBI and one 8-Gy boost; little toxicity was seen as boost time decreased [17]. Several authors have also researched weekly fractionation schedules with minimal toxicity and effective local control [4,18].

In this study, we noticed low rates of acute and late toxicity at 12 to 18 months of follow-up. There was a statistically significant difference between both arms as arm B had better outcomes regarding mean, maximum dose to heart and maximum dose to ipsilateral lung. The mean of V95% (breast volume that received 95% of the recommended dose) was 89.52%in arm A and 90.13% in arm B. The heart had a mean of 3.87Gy in arm A and 1.45Gy in arm B. Mean value for V20 of the lung (volume of the lung receiving 20Gy) was 15.12% and 14.72% in arm A and B respectively, while V30 of the heart (volume of the heart receiving30Gy) was far less, 2.86% and 2.51% in arm A and B respectively. Chadha et al. [19] reported that in >95% of plans, the lumpectomy CTV was included in≥ 95% of the prescribed dose. In 160 patients treated with whole breast irradiation 40.5Gy in 2.7Gy fractions and a concomitant lumpectomy boost of 4.5Gy in 0.3Gy fractions, median lung V20 was 7.6%, the median dose received by the heart was 215cGy and total dose to the lumpectomy site was 45Gy in fifteen fractions in a span of nineteen days.

Regarding acute toxicity after finishing and 3 months later, skin was the most frequently affected where 42 patients (70%) in arm A and 52 patients (86.67%)in arm B had skin manifestations at finishing. Forty patients (66.67%) in arm A and 46 patients (76.67%) in arm B still had symptoms at 3 months after finishing. Grade 1 and 2 toxicity were dominant at finishing, however, patients with grade 2 toxicity showed statistically significant improvement over 3 months period (from 23.33% to 10% in arm A and from 26.67% to 16.67% in arm B).

In this study there was acute grade 1 skin toxicity, in the form of erythema, edema and desquamation, in 28 patients (46.67%) in arm A and 30 patients (50%) in arm B. We reported grade 2 skin toxicity in 14 patients (23.33%) and 16 patients (26.67%) in arm A&B respectively, while no patients in arm A had grade 3 skin, six patients (10%) in arm B did. The results of a randomised trial from MD Anderson, which used the Common Terminology Criteria for Adverse Events (CTCAE), indicated acute grade two and three toxicity rates of 47% and 0% for patients receiving HF-WBI [20], this finding is consistent with our data. On the contrary, 143 patients got 42.4Gy in 16 daily fractions, 2.65Gy per fraction to the whole breast, plus an extra sequential boost to the tumour bed as observed by Linares et al. [21] and there was increased acute toxicity, where 62% showed grade 1 and 7% developed grade 2 skin toxicity. Gupta et al. [22] observed acute grade 2 in 30% of cases and grade 3 in 10% of cases, which is consistent with our results. In a study by Ahlawat et al. [23] which delivered a whole breast dose of 36.63Gy in 11 fractions of 3.33Gy followed by a tumour bed boost of 13.32Gy in 4 fractions of 3.33Gy delivered once daily over a total of fifteen treatment days (the same dose of arm B in our study), 29 patients (34%) had grade 2 acute toxicity and 1 patient had acute grade 3 toxicity.

According to Ciammella et al.'s study [24], 35 patients out of 212 had no acute toxicity, 145 (68%) had grade 1 toxicity, and 31 patients (15%) had grade 2 toxicity with whole breast irradiation dose was 40.05Gy, delivered in 15 daily fractions at a rate of 2.67Gy per fraction, with a boost to the tumour bed of 9Gy administered over the course of three consecutive fractions. Grade 1 and grade 2/grade 3 acute skin toxicity were reported to be 61.3% and 20.5%, respectively, by De Santis et al. [25] who delivered 42.4Gy in 16 daily fractions, 2.65Gy per fraction with a boost to the tumour bed in patients with close/positive margins or grade III breast cancer. This was in disagreement with our study. De Santis et al. [25]. However, Guenzi et al. [26] recorded acute grade 1/2 toxicity of 56.1%/9.8% in patients received 46Gy/20fractions, whereas 31.9% grade 1 and absence of grade 2 toxicity in those received 39Gy/13fractions.Preliminary results of UK FAST trial tested 27Gy in 5 daily fractions of 5.4Gy and 26Gy in 5 daily fractions of 5.2Gy versus 40Gy in 15 fractions. It showed mild (Grade 1) acute skin reactions in all arms [27].

With 160 patients receiving whole breast irradiation of 40.5Gy in 2.7Gy fractions and a concomitant lumpectomy boost of 4.5Gy in 0.3Gy fractions, total dose to the lumpectomy site was 45 Gy in 15 fractions over 19 days, Chadha et al. [19] discovered higher grade 1 (70%) and 2 (5%) acute skin toxicity, respectively. Contrarily, Cante et al. [28] found that patients who received whole breast irradiation of 45Gy (2.25Gy/20 fractions) with an additional daily boost of 0.25Gy to the surgical cavity (2.5Gy/20 fractions up to 50Gy) experienced no acute skin toxicity in 57% of cases, grade 1 in 40% of patients, and grade 2 in 3% of cases. The

phase 3 trial IMPORT HIGH tested a concurrent boost in addition to a risk-adapted dose design; three-way randomizations between HF-WBI with a consequent boost, reduced dose (36Gy in 15 fractions) WBI with 40Gy in 15 fractions to a partial breast volume and a concurrent lumpectomy bed boost to 48Gy, and an identical third arm with a concurrent tumour bed boost to 53Gy. Low incidence of moderate to severe (Grade 2 to Grade 4) side effects were found in recent preliminary data across all 3 arms [29,30].

There are likely discrepancies in the toxicity scales that were employed, as well as the inherent subjectivity in giving those grades, which account for the broad variation in reported skin toxicities. The reported variances could potentially be the result of variations in patient positioning, setup, and treatment methods.

Our study's and other HF-WBI courses' low rates of acute toxicity can be explained by radiobiological principles. In particular, the greater lower equivalent dose for high a/b ratio (acute toxicity) is essential to establish equivalence for low a/b ratio (breast tumour and late toxicity), leaving rapidly proliferating tissues like skin [22].

Regarding chronic toxicity in our study, in the form of hyper pigmentation and atrophy,32 patients in arm A and 38 patients in arm B still had skin manifestations at 6 months follow up, however, they were all consistent mostly with G1 changes. There was highly significant improvement in Arm A in comparison to Arm B over 12 months' follow-up as only 12 patients in arm A still had G1 manifestation at 12 months after treatment while on the other hand 24 patients in arm B had persistent symptoms.

In this study, 18 patients (30%) in arm A and 32 patients (53.67%) in arm B showed G1 breast atrophy at 6 months after treatment, however, the number decreased to only 4 patients (6.67%) in arm A and 20 patients(33.33%) in arm B by the end of the first year which showed highly statistically significant improvement. Moreover, De Santis et al. [25] documented grade 1 and grade 2/ grade 3 late fibrosis 12.6% and 4.3% of cases respectively, while with Linares et al. [17] no fibrosis grade $\geq$ 2 was noticed. On the other hand, Ciammella et al. [24] found fewer rates of grade 1 toxicity of 39 (18%) and grade 2 of 2 (1%) patients. Multiple studies claimed that there were no G3 events, and that late skin and subcutaneous damage was often mild [28]. Gupta et al. [22] analysis of late toxicity found that late grade 2 and grade 3 toxicity occurred in 1% and 3% of patients, respectively. Only two patients suffered grade 3 late skin toxicity and 1 patient experienced late grade 2 toxicity (fibrosis) in the Ahlawat et al. trial [23].

Clinical assessments of breast distortion, shrinkage, induration, edema, shoulder stiffness and telangiectasia in the RMH/GOC trial revealed significant differences at follow-up, with the 39Gy arm generally doing better and the 42.9Gy arm performing worse. The 41.6Gy and 50Gy arms of the START A study did not differ significantly at follow-up, however the 39Gy arm significantly reduced breast induration, edema, and telangiectasias compared to the 50Gy arm. There was no difference between the HF-WBI arm and the CF-WBI in terms of breast shrinkage, shoulder stiffness, or arm edema. Breast shrinkage, telangiectasias, and edema were significantly reduced in the 40Gy arm compared to the 50Gy arm at follow-up in the START B research, but there were no significant differences in breast induration, shoulder stiffness, or arm edema [31,32,33]. Our results compare favorably with the results of both START B and OCOG studies, despite changes in the grading schemes employed for late toxicity. The 30Gy or 28.5Gy in 5 once-weekly fractions versus 50Gy in 25 fractions randomised phase 3 United Kingdom (UK) FAST study found equal late toxicity between the 28.5Gy and 50Gy arms but greater toxicity in the 30Gy arm [34].

In our study, arm lymphedema stage 0-1 was present in 16 individuals in arm A and 12 patients in arm B. According to Warren et al. [35], there was no statistically significant difference between SC and SC+PAB, but the addition of regional LN radiation (RLNR) as supraclavicular SC and/or posterior axillary boost (PAB) significantly increased the risk of lymphedema compared to whole breast radiation alone (p=0.0001). In contrast, Shah et al. [36] did not notice that RLNR was a substantial risk factor for lymphedema. According to Graham et al.'s research [37], whereas increasing the field or including a PAB did cause a higher risk of lymphedema than SC volumes that were laterally constrained by the coracoid process.

Interestingly, the local recurrence rate (LRR) rates among heterogeneous groups of breast cancer patients is remarkably and uniformly low when adjuvant radiation therapy is delivered. No local recurrence was notified at follow up in this 12-18 months follow up study. At follow up of START A trial, local relapse was 6.7% in the 50Gy arm, 5.6% in the 41.6Gy arm, and 8.1% in the 39Gy arm; neither

HF-WBI arm was significantly different from the control CF-WBI arm. Similarly, distant relapse and overall survival did not significantly differ between either of the HF-WBI regimens and CF-WBI regimen. At 10 years follow up of START B trial, local relapse was 5.2% in the 50Gy arm and 3.8% in the 40Gy arm, which were not significantly different. Interestingly, distant relapse (16.0% vs. 12.3%, p=0.014) and overall mortality (19.2% vs. 15.9%, p=0.042) were significantly higher in the CF-WBI arm compared to the HF-WBI arm [38]. Most of the results showed good local and distant control due to early selection of cases and non-exceeded N1 status.

At Five –year follow up, Gupta et al. documented locoregional and distant control were 97.7% and 97.9% respectively [22]. After a median follow-up of 40 months in a study by Ahlawat et al. [23], 2 cases of isolated ipsilateral breast tumor recurrence occurred. Three-year estimated local recurrence-free survival was 95.9. The 3-year estimated distant recurrence-free survival was 97.3%. Chadha et al. [19] documented local control of 99% after a median follow-up of 3.5 years. At a median follow-up of 27 months. Hou et al. [39] reported a local control of 100%.

Another approach is testing extremely hypofractionated regimens. The randomized phase 3 United Kingdom (UK) FAST trial tested 30Gy or 28.5Gy in 5 once-weekly fractions against 50Gy in25 fractions in postmenopausal women >50 years of age after BCS with early-stage, had tumor 3 cm or less, node-negative tumors;10-year results were recently reported, demonstrating low rates of local recurrence in all arms and similar late toxicity between the 28.5Gy and 50Gy arms but increased toxicity in the 30Gy arm(worse breast appearance outcomes compared to those with 28.5 and 50Gy). With a median follow-up of 37.3 months, there were 2 local relapses and 23 deaths [34]. In addition, there are several ongoing or completed large, randomized trials investigating HF-WBI. The UK FAST-Forward trial aims to assess shortening this fractionations schedule even further, building on the UK FAST trial. The control arm of the trial is 40Gy in 15 fractions. The experiment alarms include 27Gy in 5 daily fractions of 5.4Gy and 26Gy in 5 daily fractions of 5.2Gy in a higher-risk population including younger, post-mastectomy and node-positive women. A 10- or 16-Gy boost may be added to the surgical scar or lumpectomy site. RNI is allowed. Preliminary results showed mild (Grade 1) acute skin reactions in all arms; follow-up continues for endpoints of tumor control and late toxicity [27]. The UK-HF trials have demonstrated excellent local control and cosmetic outcomes with HF WBI treatment compared to standard treatment [32,40].

In order to achieve maximal benefit from the 3-week hypofractionated schedule included sequential boost, patients must be told to abide to the pre-radiotherapy precautions. Further studies are required to standardize this protocol, especially in the old age patients, which are an area of debate. Larger multi-centric studies may be beneficial due to incorporation of higher number of patients with a liability to lengthier follow-up period.

Several limitations have been noticed at our study, including few number of patients, short time of follow up, data bias and not all patients committing the precautions during treatment, which limits comparative studies with other HF-WBI courses. Besides, points of strength are that the study is prospective, patients received regional nodal irradiation, its inclusion of high-risk patients such as young age women and negative hormone receptors, 50% and 43.33% of patients in arm A and B respectively, and the study has encouraging results.

Conclusions: A shortened 3-week HF-WBI schedule has cost, and time benefit and it is as safe, effective with low toxicity as standard 4-weeks HF-WBI and may be a sensible alternative after breast conservation surgery, although there was a significant difference between the 2 protocols regarding chronic skin toxicity as Arm A had lower skin toxicity over 12 months' follow up.

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DECELERATION OF INTEREST

The authors report no conflicts of interest.

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